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【Name of item】 Specification 1

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【Name of item】 Abstract 1

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【TYPE OF DOCUMENT】 SPECIFICATION

【TITLE OF THE INVENTION】

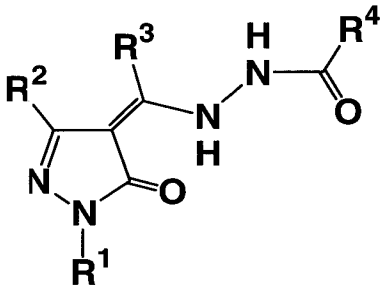
PYRAZOLONE COMPOUNDS AND THROMBOPOIETIN RECEPTOR ACTIVATOR

【SCOPE OF THE CLAIM(S)】

【Claim 1】

A pyrazolone compound represented by the formula (1)

【Ka 1】



(1)

[wherein R^1 is a C_{6-18} aryl group or a pyridyl group (the C_{6-18} aryl group and the pyridyl group may be optionally substituted with one or more C_{1-6} alkyl groups, one or more C_{1-3} alkyl groups substituted with one or more fluorine atoms, one or more halogen atoms, one or more nitro groups, one or more C_{1-6} alkylcarbonyl groups, one or more hydroxyl groups or one or more amino groups (the hydroxyl groups and the amino groups may be substituted with a C_{1-6} alkyl group or a C_{1-6} alkylcarbonyl group)), R^2 is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{6-18} aryl group, R^3 is a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms, a C_{6-18} aryl

group or a pyridyl group, and R^4 is a C_{6-18} aryl group or a pyridyl group (the C_{6-18} aryl group and the pyridyl group may be optionally substituted with one or more hydroxyl groups, one or more nitro groups, one or more carboxyl groups, one or more C_{1-6} alkoxycarbonyl groups, $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^5 (R^5 is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3) or NR^6R^7 (wherein R^6 and R^7 are independently hydrogen atoms, formyl groups, C_{1-6} alkyl groups or C_{1-6} alkylcarbonyl groups)) provided that combinations wherein R^1 is an orthochlorophenyl group, a parachlorophenyl group, an orthomethylphenyl group or a paramethylphenyl group, and R^2 is a methyl group are excluded], a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

【Claim 2】

The pyrazolone compound according to Claim 1, wherein R^4 is a C_{6-18} aryl group substituted with one or more nitro groups, a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

【Claim 3】

The pyrazolone compound according to Claim 1, wherein R^4 is a C_{6-18} aryl group substituted with one or more hydroxyl groups, a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

【Claim 4】

The pyrazolone compound according to Claim 1, wherein R^4 is a C_{6-18} aryl group substituted with one or more carboxyl groups, a tautomer, prodrug or pharmaceutically acceptable salt of the compound, or a solvate thereof.

【Claim 5】

The pyrazolone compound according to Claim 1, wherein R^4 is a C_{6-18} aryl group substituted with $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^5 (R^5 is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3), a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

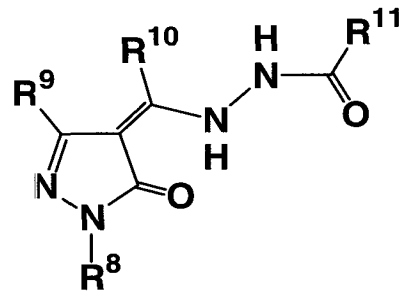
【Claim 6】

The pyrazolone compound according to Claim 1, wherein R^4 is a C_{6-18} aryl group substituted with NR^6R^7 (wherein R^6 and R^7 are independently hydrogen atoms, formyl groups, C_{1-6} alkyl groups or C_{1-6} alkylcarbonyl groups), a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof.

【Claim 7】

A thrombopoietin receptor activator represented by the formula (2)

【Ka 2】



(2)

[wherein R^8 is a C_{6-18} aryl group or a pyridyl group (the C_{6-18} aryl group and the pyridyl group may be optionally substituted with one or more C_{1-6} alkyl groups, one or more C_{1-3} alkyl groups substituted with one or more fluorine atoms, one or more halogen atoms, one or more nitro groups, one or more C_{1-6} alkylcarbonyl groups, one or more hydroxyl groups or one or more amino groups (the hydroxyl groups and the amino groups may be substituted with a C_{1-6} alkyl group or a C_{1-6} alkylcarbonyl group)), R^9 is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{6-18} aryl group, R^{10} is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms, a C_{6-18} aryl group or a pyridyl group, and R^{11} is a C_{6-18} aryl group or a pyridyl group (the C_{6-18} aryl group and the pyridyl group may be optionally substituted with one or more hydroxyl groups, one or more nitro groups, one or more carboxyl groups, one or more C_{1-6} alkoxycarbonyl groups, $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^5 (R^5 is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are

independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3) or NR^6R^7 (wherein R^6 and R^7 are independently hydrogen atoms, formyl groups, C_{1-6} alkyl groups or C_{1-6} alkylcarbonyl groups)].

【Claim 8】

The thrombopoietin receptor activator according to Claim 7, wherein R^{11} is a C_{6-18} aryl group substituted with one or more nitro groups.

【Claim 9】

The thrombopoietin receptor activator according to Claim 7, wherein R^{11} is a C_{6-18} aryl group substituted with one or more hydroxyl groups.

【Claim 10】

The thrombopoietin receptor activator according to Claim 7, wherein R^{11} is a C_{6-18} aryl group substituted with one or more carboxyl groups.

【Claim 11】

The thrombopoietin receptor activator according to Claim 7, wherein R^{11} is a C_{6-18} aryl group substituted with $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^5 (R^5 is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3).

【Claim 12】

The thrombopoietin receptor activator according to Claim 7, wherein R^{11} is a C_{6-18} aryl group substituted with NR^6R^7 (wherein R^6 and R^7 are independently hydrogen atoms,

formyl groups, C_{1-6} alkyl groups or C_{1-6} alkylcarbonyl groups).

【Claim 13】

A preventive, therapeutic or improving agent for diseases against which activation of the thrombopoietin receptor is effective, which contains the thrombopoietin receptor activator according to Claim 7, Claim 8, Claim 9, Claim 10, Claim 11 or Claim 12, a tautomer, prodrug or pharmaceutically acceptable salt of the activator or a solvate thereof, as an active ingredient.

【Claim 14】

A platelet increasing agent containing the thrombopoietin receptor activator according to Claim 7, Claim 8, Claim 9, Claim 10, Claim 11 or Claim 12, a tautomer, prodrug or pharmaceutically acceptable salt of the activator or a solvate thereof, as an active ingredient.

【DETAILED DESCRIPTION OF THE INVENTION】

【Technical Field to which the Invention Belongs】

The present invention relates to preventive, therapeutic and improving agents having affinity for and agonistic action on the thrombopoietin receptor for diseases against which activation of the thrombopoietin receptor is effective. Specifically, it relates to pharmaceutical compositions comprising compounds which increase platelets through stimulation of differentiation and proliferation of hematopoietic stem cells,

megakaryocytic progenitor cells and megakaryocytes or compounds for therapeutic angiogenesis or with anti-arteriosclerosis action that stimulate differentiation and proliferation of vascular endothelial cells and endothelial progenitor cells.

【Prior Art】

Thrombopoietin is a cytokine consisting of 332 amino acids that increases platelet production by stimulating differentiation and proliferation of hematopoietic stem cells, megakaryocytic progenitor cells and megakaryocytes mediated by its receptor and therefore is promising as a drug for hematological disorders. Recent reports that it stimulates differentiation and proliferation of vascular endothelial cells and endothelial progenitor cells have raised expectations of therapeutic angiogenesis, anti-arteriosclerosis and prevention of cardiovascular events (for example, non-patent document 1, non-patent document 2 and non-patent document 3).

Biologically active substances which have been known so far to regulate platelet production through the thrombopoietin receptor include, in addition to thrombopoietin itself, low molecular weight peptides having affinity for the thrombopoietin receptor (for example, patent document 1, patent document 2, patent document 3 and patent document 4).

As a result of search for nonpeptidic low molecular weight compounds that increase platelet production

mediated by the thrombopoietin receptor, low molecular weight compounds having affinity for the thrombopoietin receptor have been reported (for example, patent document 5 to patent document 18).

1) Applications filed by Hokuriku Seiyaku Co., Ltd. relating to 1,4-benzodiazepine derivatives (patent documents 5 and 6)

2) International Laid-open Patent Applications filed by Shionogi & Co., Ltd. (patent documents 7 and 8)

3) International Laid-open Patent Applications filed by SmithKline Beecham Corp (patent documents 9-16)

4) Japanese Laid-open Patent Application filed by Torii Pharmaceutical Co., Ltd. (patent document 17)

5) International Laid-open Patent Application filed by Roche Diagnostics GMBH (patent document 18)

Some reports have been made about pyrazolone compounds (such as non-patent documents 4-7).

In addition, pyrazolone compounds having an orthochlorophenyl group, a parachlorophenyl group, an orthomethylphenyl group or a paramethylphenyl group as a substituent on the nitrogen atom of pyrazolone have been reported as intermediates for polymer materials excellent as pigments (for example, patent document 20).

【Patent Document 1】

JP-A-10-72492

【Patent Document 2】

WO96/40750

【Patent Document 3】

WO96/40189

【Patent Document 4】

WO98/25965

【Patent Document 5】

JP-A-11-1477

【Patent Document 6】

JP-A-11-152276

【Patent Document 7】

WO01/07423

【Patent Document 8】

WO01/53267

【Patent Document 9】

WO00/35446

【Patent Document 10】

WO00/66112

【Patent Document 11】

WO01/34585

【Patent Document 12】

WO01/17349

【Patent Document 13】

WO01/39773

【Patent Document 14】

WO01/21180

【Patent Document 15】

WO01/89457

【Patent Document 16】

WO02/49413

【Patent Document 17】

JP-A-2001-97948

【Patent Document 18】

WO99/11262

【Patent Document 19】

EP-A-349489

【Patent document 20】

JP-A-02-110145

【Non-patent Document 1】

Microvasc Res 1999: 58, p.108-113

【Non-patent Document 2】

Circ Res 1999: 84, p.785-796

【Non-patent Document 3】

Blood 2001:98, p.71a

【Non-patent Document 4】

Huaxue Xuebao (2001), 59(9) p.1495-1501

【Non-patent Document 5】

Synthesis and Reactivity in Inorganic and Metal Organic Chemistry (2000), 30(7) p.1265-1271

【Non-patent Document 6】

Pclyhedroon (1997), 16(11) p.1825-1829

【Non-patent Document 7】

Arzneim-Forsch (1969), 19(10) p.1721-1723

【Problems that the Invention is to Solve】

Thrombopoietin and low molecular weight peptides

having affinity for the thrombopoietin receptor are likely to be easily degraded in the gastrointestinal tract and are usually difficult to orally administer. As to thrombopoietin itself, the appearance of anti-thrombopoietin antibodies have been reported.

Besides, though it is probably possible to orally administer nonpeptidic low molecular weight compounds, no practical drugs have been put on the market.

Therefore, orally administrable low molecular weight compounds having excellent affinity for and agonistic action on the thrombopoietin receptor as preventive, therapeutic and improving agents for diseases against which activation of the thrombopoietin receptor is effective have been demanded. Specifically, low molecular weight compounds which can serve as platelet increasing agents or increasing agents for other blood cells by stimulating differentiation and proliferation of hematopoietic stem cells, megakaryocytic progenitor cells and megakaryocytes or low molecular weight compounds which can be used for therapeutic angiogenesis or as preventive and therapeutic agents for arteriosclerosis by stimulating endothelial cells and endothelial progenitor cells have been demanded.

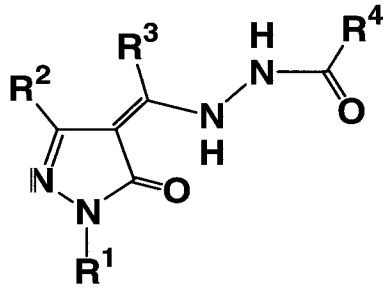
【Means of Solving the Problems】

The present inventors conducted extensive research to find low molecular weight compounds having affinity for and agonistic action on the thrombopoietin receptor, and

as a result, found that the compounds of the present invention have high affinity and agonistic action which enable them to show potent platelet increasing action by stimulating differentiation and proliferation of megakaryocytic progenitor cells and megakaryocytes. The present invention was accomplished on the basis of this discovery.

Namely, the present invention relates to a pyrazolone compound represented by the formula (1)

【Ka 3】

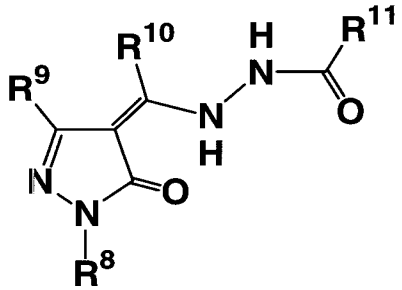


(1)

[wherein R^1 is a C_{6-18} aryl group or a pyridyl group (the C_{6-18} aryl group and the pyridyl group may be optionally substituted with one or more C_{1-6} alkyl groups, one or more C_{1-3} alkyl groups substituted with one or more fluorine atoms, one or more halogen atoms, one or more nitro groups, one or more C_{1-6} alkylcarbonyl groups, one or more hydroxyl groups or one or more amino groups (the hydroxyl groups and the amino groups may be substituted with a C_{1-6} alkyl group or a C_{1-6} alkylcarbonyl group)), R^2 is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{6-18} aryl group, R^3 is a C_{1-6} alkyl group, a C_{1-3} alkyl group

substituted with one or more fluorine atoms, a C_{6-18} aryl group or a pyridyl group, and R^4 is a C_{6-18} aryl group or a pyridyl group (the C_{6-18} aryl group and the pyridyl group may be optionally substituted with one or more hydroxyl groups, one or more nitro groups, one or more carboxyl groups, one or more C_{1-6} alkoxycarbonyl groups, $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^5 (R^5 is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3) or NR^6R^7 (wherein R^6 and R^7 are independently hydrogen atoms, formyl groups, C_{1-6} alkyl groups or C_{1-6} alkylcarbonyl groups)) provided that combinations wherein R^1 is an orthochlorophenyl group, a parachlorophenyl group, an orthomethylphenyl group or a paramethylphenyl group, and R^2 is a methyl group are excluded], a tautomer, prodrug or pharmaceutically acceptable salt of the compound or a solvate thereof. It also relates to a thrombopoietin receptor activator represented by the formula (2)

【Ka 4】



(2)

[wherein R^8 is a C_{6-18} aryl group or a pyridyl group (the C_{6-18} aryl group and the pyridyl group may be optionally

substituted with one or more C_{1-6} alkyl groups, one or more C_{1-3} alkyl groups substituted with one or more fluorine atoms, one or more halogen atoms, one or more nitro groups, one or more C_{1-6} alkylcarbonyl groups, one or more hydroxyl groups or one or more amino groups (the hydroxyl groups and the amino groups may be substituted with a C_{1-6} alkyl group or a C_{1-6} alkylcarbonyl group)), R^9 is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{6-18} aryl group, R^{10} is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms, a C_{6-18} aryl group or a pyridyl group, and R^{11} is a C_{6-18} aryl group or a pyridyl group (the C_{6-18} aryl group and the pyridyl group may be optionally substituted with one or more hydroxyl groups, one or more nitro groups, one or more carboxyl groups, one or more C_{1-6} alkoxycarbonyl groups, $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^5 (R^5 is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3) or NR^6R^7 (wherein R^6 and R^7 are independently hydrogen atoms, formyl groups, C_{1-6} alkyl groups or C_{1-6} alkylcarbonyl groups))], a preventive, therapeutic or improving agent for diseases against which activation of the thrombopoietin receptor is effective which contains the thrombopoietin receptor activator, a tautomer, prodrug or pharmaceutically acceptable salt of

the thrombopoietin receptor activator or a solvate thereof as an active ingredient, and a platelet increasing agent containing the thrombopoietin receptor activator, a tautomer, prodrug or pharmaceutically acceptable salt of the thrombopoietin receptor activator or a solvate thereof as an active ingredient.

Though WO99/11262 (patent document 18), WO01/34585 (patent document 11), WO02/49413 (patent document 16) disclose pyrazolone compounds having platelet increasing action, there is no specific disclosure of the pyrazolone compounds of the present invention. The compounds of the present invention showed high activity that could not be expected from the disclosure in WO99/11262 (patent document 18), WO01/34585 (patent document 11) or WO02/49413 (patent document 16).

【Mode of Carrying out the Invention】

Now, the present invention will be described in detail.

In the present invention, "n" denotes normal, "i" denotes iso, "s" denotes secondary, "t" denotes tertiary, "c" denotes cyclo, "o" denotes ortho, "m" denotes meta, "p" denotes para, "Ph" denotes phenyl, "Py" denotes pyridyl, "Naphthyl" denotes naphthyl, "Me" denotes methyl, "Et" denotes ethyl, "Pr" denotes propyl, and "Bu" denotes butyl.

First, the terms in the respective substituents R^1, R^2, R^3, R^4, R^8, R^9, R^{10} and R^{11} will be explained.

As a halogen atom, fluorine, chlorine, bromine or iodine may be mentioned.

A C_{1-3} alkyl group may be linear, branched or cyclic, and methyl, ethyl, n-propyl, i-propyl and c-propyl and the like may be mentioned. As a C_{1-6} alkyl group, in addition to those mentioned above, n-butyl, i-butyl, s-butyl, t-butyl, c-butyl, 1-methyl-c-propyl, 2-methyl-c-propyl, n-pentyl, 1-methyl-n-butyl, 2-methyl-n-butyl, 3-methyl-n-butyl, 1,1-dimethyl-n-propyl, 1,2-dimethyl-n-propyl, 2,2-dimethyl-n-propyl, 1-ethyl-n-propyl, c-pentyl, 1-methyl-c-butyl, 2-methyl-c-butyl, 3-methyl-c-butyl, 1,2-dimethyl-c-propyl, 2,3-dimethyl-c-propyl, 1-ethyl-c-propyl, 2-ethyl-c-propyl, n-hexyl, 1-methyl-n-pentyl, 2-methyl-n-pentyl, 3-methyl-n-pentyl, 4-methyl-n-pentyl, 1,1-dimethyl-n-butyl, 1,2-dimethyl-n-butyl, 1,3-dimethyl-n-butyl, 2,2-dimethyl-n-butyl, 2,3-dimethyl-n-butyl, 3,3-dimethyl-n-butyl, 1-ethyl-n-butyl, 2-ethyl-n-butyl, 1,1,2-trimethyl-n-propyl, 1,2,2-trimethyl-n-propyl, 1-ethyl-1-methyl-n-propyl, 1-ethyl-2-methyl-n-propyl, c-hexyl, 1-methyl-c-pentyl, 2-methyl-c-pentyl, 3-methyl-c-pentyl, 1-ethyl-c-butyl, 2-ethyl-c-butyl, 3-ethyl-c-butyl, 1,2-dimethyl-c-butyl, 1,3-dimethyl-c-butyl, 2,2-dimethyl-c-butyl, 2,3-dimethyl-c-butyl, 2,4-dimethyl-c-butyl, 3,3-dimethyl-c-butyl, 1-n-propyl-c-propyl, 2-n-propyl-c-propyl, 1-i-propyl-c-propyl, 2-i-propyl-c-propyl, 1,2,2-trimethyl-c-propyl, 1,2,3-trimethyl-c-propyl, 2,2,3-trimethyl-c-propyl, 1-ethyl-2-

methyl-c-propyl, 2-ethyl-1-methyl-c-propyl, 2-ethyl-2-methyl-c-propyl, 2-ethyl-3-methyl-c-propyl and the like may be mentioned.

As a C_{6-18} aryl group containing no hetero atoms, a phenyl group, a 1-indenyl group, a 2-indenyl group, a 3-indenyl group, a 4-indenyl group, a 5-indenyl group, a 6-indenyl group, a 7-indenyl group, an α-naphthyl group, a β-naphthyl group, a 1-tetrahydronaphthyl group, a 2-tetrahydronaphthyl group, a 5-tetrahydronaphthyl group, a 6-tetrahydronaphthyl group, an o-biphenyl group, a m-biphenyl group, a p-biphenyl group, a 1-anthryl group, a 2-anthryl group, a 9-anthryl group, a 1-phenanthryl group, a 2-phenanthryl group, a 3-phenanthryl group, a 4-phenanthryl group, a 9-phenanthryl group or the like may be mentioned.

A C_{1-3} alkyl group substituted with one or more fluorine atoms may be a trifluoromethyl group, a difluoromethyl group, a monofluoromethyl group, a pentafluoroethyl group, a 1,1-difluoro-2,2-difluoroethyl group, a heptafluoropropyl group or the like.

A C_{1-6} alkylcarbonyl group may be methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, i-propylcarbonyl, n-butylcarbonyl, i-butylcarbonyl, s-butylcarbonyl, t-butylcarbonyl, n-pentylcarbonyl, 1-methyl-n-butylcarbonyl, 2-methyl-n-butylcarbonyl, 3-methyl-n-butylcarbonyl, 1,1-dimethyl-n-propylcarbonyl, 1,2-dimethyl-n-propylcarbonyl, 2,2-dimethyl-n-propylcarbonyl,

1-ethyl-n-propylcarbonyl, n-hexylcarbonyl, 1-methyl-n-pentylcarbonyl, 2-methyl-n-pentylcarbonyl, 3-methyl-n-pentylcarbonyl, 4-methyl-n-pentylcarbonyl, 1,1-dimethyl-n-butylcarbonyl, 1,2-dimethyl-n-butylcarbonyl, 1,3-dimethyl-n-butylcarbonyl, 2,2-dimethyl-n-butylcarbonyl, 2,3-dimethyl-n-butylcarbonyl, 3,3-dimethyl-n-butylcarbonyl, 1-ethyl-n-butylcarbonyl, 2-ethyl-n-butylcarbonyl, 1,1,2-trimethyl-n-propylcarbonyl, 1,2,2-trimethyl-n-propylcarbonyl, 1-ethyl-1-methyl-n-propylcarbonyl, 1-ethyl-2-methyl-n-propylcarbonyl or the like.

A C_{1-6} alkoxycarbonyl group may be methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, i-propoxycarbonyl, n-butoxycarbonyl, i-butoxycarbonyl, s-butoxycarbonyl, t-butoxycarbonyl, n-pentyloxycarbonyl, 1-methyl-n-butoxycarbonyl, 2-methyl-n-butoxycarbonyl, 3-methyl-n-butoxycarbonyl, 1,1-dimethyl-n-propoxycarbonyl, 1,2-dimethyl-n-propoxycarbonyl, 2,2-dimethyl-n-propoxycarbonyl, 1-ethyl-n-propoxycarbonyl, n-hexyloxycarbonyl, 1-methyl-n-pentyloxycarbonyl, 2-methyl-n-pentyloxycarbonyl, 3-methyl-n-pentyloxycarbonyl, 4-methyl-n-pentyloxycarbonyl, 1,1-dimethyl-n-butoxycarbonyl, 1,2-dimethyl-n-butoxycarbonyl, 1,3-dimethyl-n-butoxycarbonyl, 2,2-dimethyl-n-butoxycarbonyl, 2,3-dimethyl-n-butoxycarbonyl, 3,3-dimethyl-n-butoxycarbonyl, 1-ethyl-n-butoxycarbonyl, 2-ethyl-n-butoxycarbonyl, 1,1,2-trimethyl-n-propoxycarbonyl, 1,2,2-

trimethyl-n-propoxycarbonyl, 1-ethyl-1-methyl-n-propoxycarbonyl, 1-ethyl-2-methyl-n-propoxycarbonyl or the like.

Specific preferred examples of the substituent R^1 are a phenyl group, a naphthalene group and pyridyl groups substituted with one or more of the following substituents.

Substituents: a C_{1-6} alkyl group, a halogen atom, a C_{1-3} alkyl group substituted with one or more fluorine atoms, a nitro group, an amino group, an amino group substituted with a C_{1-6} alkyl group, an amino group substituted with a C_{1-6} alkylcarbonyl group, a hydroxyl group, a hydroxyl group substituted with a C_{1-6} alkyl group, a hydroxyl group substituted with a C_{1-6} alkylcarbonyl group and a C_{1-6} alkylcarbonyl group.

Particularly preferred examples of the substituent R^1 are a 3-methyl-phenyl group, a 4-methyl-phenyl group, a 3,4-dimethyl-phenyl group, a 3-t-butyl-phenyl group, a 4-t-butyl-phenyl group, a 3-trifluoromethyl-phenyl group, a 4-trifluoromethyl-phenyl group, a 3,4-ditrifluoromethyl-phenyl group, a 3-chloro-phenyl group, a 4-chloro-phenyl group, a 3-iodo-phenyl group, a 4-iodo-phenyl group, a 3-fluoro-phenyl group, a 4-fluoro-phenyl group, a 3,4-dichloro-phenyl group, a 3,4-diiode-phenyl group, a 3,4-difluoro-phenyl group, a 3-nitro-phenyl group, a 4-nitro-phenyl group and the like.

Specific preferred examples of the substituent R^8 are

a phenyl group, a naphthalene group and pyridyl groups which are not substituted or substituted with one or more of the following substituents.

Substituents: a C_{1-6} alkyl group, a halogen atom, a C_{1-3} alkyl group substituted with one or more fluorine atoms, a nitro group, an amino group, an amino group substituted with a C_{1-6} alkyl group, an amino group substituted with a C_{1-6} alkylcarbonyl group, a hydroxyl group, a hydroxyl group substituted with a C_{1-6} alkyl group, a hydroxyl group substituted with a C_{1-6} alkylcarbonyl group and a C_{1-6} alkylcarbonyl group.

Particularly preferred examples of the substituent R^8 are a phenyl group, a 3-methyl-phenyl group, a 4-methyl-phenyl group, a 3,4-dimethyl-phenyl group, a 3-t-butyl-phenyl group, a 4-t-butyl-phenyl group, a 3-trifluoromethyl-phenyl group, a 4-trifluoromethyl-phenyl group, a 3,4-ditrifluoromethyl-phenyl group, a 3-chloro-phenyl group, a 4-chloro-phenyl group, a 3-iodo-phenyl group, a 4-iodo-phenyl group, a 3-fluoro-phenyl group, a 4-fluoro-phenyl group, a 3,4-dichloro-phenyl group, a 3,4-diiode-phenyl group, a 3,4-difluoro-phenyl group, a 3-nitro-phenyl group, a 4-nitro-phenyl group, a 1-naphthyl group, a 2-naphthyl group, a 2-pyridyl group, a 3-pyridyl group, a 4-pyridyl group and the like.

Specific preferable examples of the substituents R^2 and R^9 are a hydrogen atom, a methyl group, an ethyl group, a n-propyl group, an i-propyl group and a

trifluoromethyl group, and a particularly preferred example is a methyl group.

Specific preferable examples of the substituent R^3 are a methyl group, an ethyl group, a n-propyl group, an i-propyl group and a trifluoromethyl group, and particularly preferable examples are a methyl group and a trifluoromethyl group.

Specific preferable examples of the substituent R^{10} are a hydrogen atom, a methyl group, an ethyl group, a n-propyl group, an i-propyl group and a trifluoromethyl group, and particularly preferred examples are a hydrogen atom, a methyl group, an ethyl group and a trifluoromethyl group.

Specific preferable examples of the substituents R^4 and R^{11} are a phenyl group, a naphthalene group and pyridyl groups substituted with one or more of the following substituents.

Substituents: a hydroxyl group, an amino group, a nitro group, a carboxyl group, CH_2CO_2H, OCH_2CO_2H, $NHCH_2CO_2H$ and $CH_2CH_2CO_2H$.

A specific particularly preferred example of the substituents R^4 and R^{11} is a phenyl group substituted with one or more of the following substituents.

Substituents: a hydroxyl group, an amino group, a nitro group, a carboxyl group, CH_2CO_2H, OCH_2CO_2H, $NHCH_2CO_2H$ and $CH_2CH_2CO_2H$.

Favorable compounds as the thrombopoietin receptor

activator, the preventive, therapeutic or improving agent for diseases against which activation of the thrombopoietin receptor is effective and the platelet increasing agent of the present invention are as follows.

1) Pyrazolone compounds represented by the formula (1) wherein R^4 is a C_{6-18} aryl group substituted with one or more nitro groups, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

2) Pyrazolone compounds represented by the formula (1) wherein R^4 is a C_{6-18} aryl group substituted with one or more hydroxyl groups, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

3) Pyrazolone compounds represented by the formula (1) wherein R^4 is a C_{6-18} aryl group substituted with a carboxyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

4) Pyrazolone compounds represented by the formula (1) wherein R^4 is a C_{6-18} aryl group substituted with $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^5 (R^5 is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1,2 or 3), tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

5) Pyrazolone compounds represented by the formula (1)

wherein R^4 is a C_{6-18} aryl group substituted with NR^6R^7 (wherein R^6 and R^7 are independently hydrogen atoms, formyl groups, C_{1-6} alkyl groups or C_{1-6} alkylcarbonyl groups), tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

6) Pyrazolone compounds represented by the formula (1) wherein R^4 is a C_{6-18} aryl group substituted with $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^5 (R^5 is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3) and with a hydroxyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

7) Pyrazolone compounds represented by the formula (1) wherein R^4 is a C_{6-18} aryl group substituted with $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^5 (R^5 is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3) and with an amino group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

8) Pyrazolone compounds represented by the formula (1) wherein R^4 is a C_{6-18} aryl group substituted with a hydroxyl group and with a carboxyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the

compounds or solvates thereof.

9) The pyrazolone compounds according to 1), 2), 3), 4), 5), 6), 7) or 8) or represented by the formula (1), wherein R^2 is a methyl group substituted with one or more fluorine atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

10) The pyrazolone compounds according to 1), 2), 3), 4), 5), 6), 7) or 8) or represented by the formula (1), wherein R^2 is a methyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

11) The pyrazolone compounds according to 1), 2), 3), 4), 5), 6), 7) or 8) or represented by the formula (1), wherein R^2 is hydrogen, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

12) The pyrazolone compounds according to 9), 10) or 11), wherein R^3 is a methyl group substituted with one or more fluorine atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

13) The pyrazolone compounds according to 9), 10) or 11), wherein R^3 is a methyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

14) The pyrazolone compounds according to 12) or 13), wherein R^1 is a phenyl group substituted with one or more C_{1-6} alkyl groups, tautomers, prodrugs or pharmaceutically

acceptable salts of the compounds or solvates thereof.

15) The pyrazolone compounds according to 12) or 13), wherein R^1 is a phenyl group substituted with one or more halogen atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

16) The pyrazolone compounds according to 12) or 13), wherein R^1 is a phenyl group substituted with one or more methyl groups substituted with one or more fluorine atoms, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

17) The pyrazolone compounds according to 12) or 13), wherein R^1 is a phenyl group substituted with a hydroxyl group substituted with a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

18) The pyrazolone compounds according to 12) or 13), wherein R^1 is a phenyl group substituted with an amino group substituted with a C_{1-6} alkyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

19) The pyrazolone compounds according to 12) or 13), wherein R^1 is a phenyl group substituted with a hydroxyl group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

20) The pyrazolone compounds according to 12) or 13), wherein R^1 is a phenyl group substituted with an amino

group substituted with a C_{1-6} alkylcarbonyl group, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

21) Thrombopoietin receptor activators represented by the formula (2) wherein R^{11} is a C_{6-18} aryl group substituted with one or more nitro groups.

22) Thrombopoietin receptor activators represented by the formula (2) wherein R^{11} is a C_{6-18} aryl group substituted with one or more hydroxyl groups.

23) Thrombopoietin receptor activators represented by the formula (2) wherein R^{11} is a C_{6-18} aryl group substituted with a carboxyl group.

24) Thrombopoietin receptor activators represented by the formula (2) wherein R^{11} is a C_{6-18} aryl group substituted with $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^5 (R^5 is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1,2 or 3).

25) Thrombopoietin receptor activators represented by the formula (2) wherein R^{11} is a C_{6-18} aryl group substituted with NR^6R^7 (wherein R^6 and R^7 are independently hydrogen atoms, formyl groups, C_{1-6} alkyl groups or C_{1-6} alkylcarbonyl groups).

26) Thrombopoietin receptor activators represented by the formula (2) wherein R^{11} is a C_{6-18} aryl group substituted with $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^5 (R^5 is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6}

alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3) and with a hydroxyl group.

27) Thrombopoietin receptor activators represented by the formula (2) wherein R^{11} is a C_{6-18} aryl group substituted with $X(CYZ)_nCO_2H$ (wherein X is CH_2, O, S or NR^5 (R^5 is a hydrogen atom, a C_{1-6} alkyl group, a formyl group or a C_{1-6} alkylcarbonyl group), Y and Z are independently hydrogen atoms or C_{1-3} alkyl groups, and n is 0, 1, 2 or 3) and with an amino group.

28) Thrombopoietin receptor activators represented by the formula (2) wherein R^{11} is a C_{6-18} aryl group substituted with a hydroxyl group and with a carboxyl group.

29) The thrombopoietin receptor activators according to 21), 22), 23), 24), 25), 26), 27) or 28) or represented by the formula (2), wherein R^9 is a methyl group substituted with one or more fluorine atoms.

30) The thrombopoietin receptor activators according to 21), 22), 23), 24), 25), 23), 27) or 28) or represented by the formula (2), wherein R^9 is a methyl group.

31) The thrombopoietin receptor activators according to 21), 22), 23), 24), 25), 26), 27) or 28) or represented by the formula (2), wherein R^9 is a hydrogen atom.

32) The thrombopoietin receptor activators according to 29), 30) or 31), wherein R^{10} is a methyl group substituted with one or more fluorine atoms.

33) The thrombopoietin receptor activators according to

29), 30) or 31), wherein R^{10} is a methyl group.

34) The thrombopoietin receptor activators according to 29), 30) or 31), wherein R^{10} is a hydrogen atom.

35) The thrombopoietin receptor activators according to 32), 33) or 34), wherein R^{8} is a phenyl group substituted with one or more C_{1-6} alkyl groups.

36) The thrombopoietin receptor activators according to 32), 33) or 34), wherein R^{8} is a phenyl group substituted with one or more halogen atoms.

37) The thrombopoietin receptor activators according to 32), 33) or 34), wherein R^{8} is a phenyl group substituted with one or more methyl groups substituted with one or more fluorine atoms.

38) The thrombopoietin receptor activators according to 32), 33) or 34), wherein R^{8} is a phenyl group substituted with a hydroxyl group substituted with a C_{1-6} alkyl group.

39) The thrombopoietin receptor activators according to 32), 33) or 34), wherein R^{8} is a phenyl group substituted with an amino group substituted with a C_{1-6} alkyl group.

40) The thrombopoietin receptor activators according to 32), 33) or 34), wherein R^{8} is a phenyl group substituted with a hydroxyl group substituted with a C_{1-6} alkylcarbonyl group.

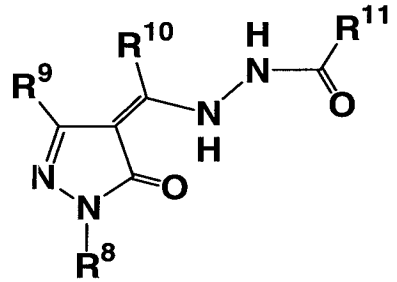
41) The thrombopoietin receptor activators according to 32), 33) or 34), wherein R^{8} is a phenyl group substituted with an amino group substituted with a C_{1-6} alkylcarbonyl group.

42) Preventive, therapeutic and improving agents for diseases against which activation of the thrombopoietin receptor is effective which contain the thrombopoietin receptor activators represented by any of 21) to 41) or the formula (2), tautomers, prodrugs or pharmaceutically acceptable salts of the activators or solvates thereof, as an active ingredient.

43) Platelet increasing agents containing the thrombopoietin receptor activators represented by any of 21) to 41) or the formula (2), tautomers, prodrugs or pharmaceutically acceptable salts of the activators or solvates thereof, as an active ingredient.

44) Preventive, therapeutic or improving agents for diseases against which activation of the thrombopoietin receptor is effective or platelet increasing agents, which contain thrombopoietin receptor activators wherein R^8, R^9, R^{10} and R^{11} are any of the following combinations in Table 1, tautomers, prodrugs or pharmaceutically acceptable salts of the activators or solvates thereof, as an active ingredient.

【Ka 5】



Compounds wherein R^8=Ph, R^9=Me, R^{10}=Me, and R^{11} is any one

of the substituents shown below.

【Hyo 1】

Table 1-1

R^{11}	Compound No.
R^{11}= 2-OH-Ph	Compound 1
R^{11}= 3-OH-Ph	Compound 2
R^{11}= 4-OH-Ph	Compound 3
R^{11}= 3, 4-$(OH)_2$-Ph	Compound 4
R^{11}= 2, 4-$(OH)_2$-Ph	Compound 5
R^{11}= 3, 5-$(OH)_2$-Ph	Compound 6
R^{11}= 2, 3-$(OH)_2$-Ph	Compound 7
R^{11}= 2, 5-$(OH)_2$-Ph	Compound 8
R^{11}= 3-NO_2-Ph	Compound 9
R^{11}= 2-NH_2-Ph	Compound 10
R^{11}= 3-NH_2-Ph	Compound 11
R^{11}= 4-NH_2-Ph	Compound 12
R^{11}= 2-CO_2H-Ph	Compound 13
R^{11}= 3-CO_2H-Ph	Compound 14
R^{11}= 4-CO_2H-Ph	Compound 15
R^{11}= 2-OCH_2CO_2H-Ph	Compound 16
R^{11}= 3-OCH_2CO_2H-Ph	Compound 17
R^{11}= 4-OCH_2CO_2H-Ph	Compound 18
R^{11}= 2-CH_2CO_2H-Ph	Compound 19
R^{11}= 3-CH_2CO_2H-Ph	Compound 20
R^{11}= 4-CH_2CO_2H-Ph	Compound 21

R^{11}= 2-$NHCH_2CO_2H$-Ph Compound 22

R^{11}= 3-$NHCH_2CO_2H$-Ph Compound 23

R^{11}= 4-$NHCH_2CO_2H$-Ph Compound 24

R^{11}= 2-$(CH_2)_2CO_2H$-Ph Compound 25

R^{11}= 3-$(CH_2)_2CO_2H$-Ph Compound 26

R^{11}= 4-$(CH_2)_2CO_2H$-Ph Compound 27

R^{11}= 4-OCH_2CO_2H-3-OH-Ph Compound 28

R^{11}= 4-OCH_2CO_2H-2-OH-Ph Compound 29

R^{11}= 3-OCH_2CO_2H-4-OH-Ph Compound 30

R^{11}= 2-OCH_2CO_2H-4-OH-Ph Compound 31

R^{11}= 3-OCH_2CO_2H-2-OH-Ph Compound 32

R^{11}= 2-OCH_2CO_2H-3-OH-Ph Compound 33

R^{11}= 4-$NHCH_2CO_2H$-3-OH-Ph Compound 34

R^{11}= 4-$NHCH_2CO_2H$-2-OH-Ph Compound 35

R^{11}= 3-$NHCH_2CO_2H$-4-OH-Ph Compound 36

R^{11}= 2- $NHCH_2CO_2H$-4-OH-Ph Compound 37

R^{11}= 3-$NHCH_2CO_2H$-2-OH-Ph Compound 38

R^{11}= 2-$NHCH_2CO_2H$-3-OH-Ph Compound 39

R^{11}= 4-OCH_2CO_2H-3-NH_2-Ph Compound 40

R^{11}= 4-OCH_2CO_2H-2-NH_2-Ph Compound 41

R^{11}= 3-OCH_2CO_2H-4-NH_2-Ph Compound 42

R^{11}= 2-OCH_2CO_2H-4-NH_2-Ph Compound 43

R^{11}= 3-OCH_2CO_2H-2-NH_2-Ph Compound 44

R^{11}= 2-OCH_2CO_2H-3-NH_2-Ph Compound 45

R^{11}= 4-$NHCH_2CO_2H$-3-NH_2-Ph Compound 46

R^{11}= 4-$NHCH_2CO_2H$-2-NH_2-Ph Compound 47

R^{11}= 3-$NHCH_2CO_2H$-4-NH_2-Ph Compound 48

R^{11}= 2-$NHCH_2CO_2H$-4-NH_2-Ph	Compound 49
R^{11}= 3-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 50
R^{11}= 2-$NHCH_2CO_2H$-3-NH_2-Ph	Compound 51
R^{11}= 4-$(CH_2)_2CO_2H$-3-OH-Ph	Compound 52
R^{11}= 4-$(CH_2)_2CO_2H$-2-OH-Ph	Compound 53
R^{11}= 2-CO_2H-4-OH-Ph	Compound 54
R^{11}= 2-CO_2H-3-OH-Ph	Compound 55
R^{11}= 4-CO_2H-2-OH-Ph	Compound 56
R^{11}= 4-CO_2H-3-OH-Ph	Compound 57
R^{11}= 3-OH-2-Naphthyl	Compound 58
R^{11}= 2-NO_2-Ph	Compound 59
R^{11}= 4-NO_2-Ph	Compound 60

Compounds wherein R^8=4-t-Bu-Ph, R^9=Me, R^{10}=Me, and R^{11} is any one of the substituents shown below.

【Hyo 2】

Table 1-2

R^{11}	Compound No.
R^{11}= 2-OH-Ph	Compound 61
R^{11}= 3-OH-Ph	Compound 62
R^{11}= 4-OH-Ph	Compound 63
R^{11}= 3,4-$(OH)_2$-Ph	Compound 64
R^{11}= 2,4-$(OH)_2$-Ph	Compound 65
R^{11}= 3,5-$(OH)_2$-Ph	Compound 66

R^{11}= 2, 3-$(OH)_2$-Ph	Compound 67
R^{11}= 2, 5-$(OH)_2$-Ph	Compound 68
R^{11}= 3-NO_2-Ph	Compound 69
R^{11}= 2-NH_2-Ph	Compound 70
R^{11}= 3-NH_2-Ph	Compound 71
R^{11}= 4-NH_2-Ph	Compound 72
R^{11}= 2-CO_2H-Ph	Compound 73
R^{11}= 3-CO_2H-Ph	Compound 74
R^{11}= 4-CO_2H-Ph	Compound 75
R^{11}= 2-OCH_2CO_2H-Ph	Compound 76
R^{11}= 3-OCH_2CO_2H-Ph	Compound 77
R^{11}= 4-OCH_2CO_2H-Ph	Compound 78
R^{11}= 2-CH_2CO_2H-Ph	Compound 79
R^{11}= 3-CH_2CO_2H-Ph	Compound 80
R^{11}= 4-CH_2CO_2H-Ph	Compound 81
R^{11}= 2-$NHCH_2CO_2H$-Ph	Compound 82
R^{11}= 3-$NHCH_2CO_2H$-Ph	Compound 83
R^{11}= 4-$NHCH_2CO_2H$-Ph	Compound 84
R^{11}= 2-$(CH_2)_2CO_2H$-Ph	Compound 85
R^{11}= 3-$(CH2)_2CO_2H$-Ph	Compound 86
R^{11}= 4-$(CH_2)_2CO_2H$-Ph	Compound 87
R^{11}= 4-OCH_2CO_2H-3-OH-Ph	Compound 88
R^{11}= 4-OCH_2CO_2H-2-OH-Ph	Compound 89
R^{11}= 3-OCH_2CO_2H-4-OH-Ph	Compound 90
R^{11}= 2-OCH_2CO_2H-4-OH-Ph	Compound 91
R^{11}= 3-OCH_2CO_2H-2-OH-Ph	Compound 92
R^{11}= 2-OCH_2CO_2H-3-OH-Ph	Compound 93

R^{11}= 4-$NHCH_2CO_2H$-3-OH-Ph Compound 94

R^{11}= 4-$NHCH_2CO_2H$-2-OH-Ph Compound 95

R^{11}= 3-$NHCH_2CO_2H$-4-OH-Ph Compound 96

R^{11}= 2-$NHCH_2CO_2H$-4-OH-Ph Compound 97

R^{11}= 3-$NHCH_2CO_2H$-2-OH-Ph Compound 98

R^{11}= 2-$NHCH_2CO_2H$-3-OH-Ph Compound 99

R^{11}= 4-OCH_2CO_2H-3-NH2-Ph Compound 100

R^{11}= 4-OCH_2CO_2H-2-NH2-Ph Compound 101

R^{11}= 3-OCH_2CO_2H-4-NH2-Ph Compound 102

R^{11}= 2-OCH_2CO_2H-4-NH_2-Ph Compound 103

R^{11}= 3-OCH_2CO_2H-2-NH_2-Ph Compound 104

R^{11}= 2-OCH_2CO_2H-3-NH_2-Ph Compound 105

R^{11}= 4-$NHCH_2CO_2H$-3-NH_2-Ph Compound 106

R^{11}= 4-$NHCH_2CO_2H$-2-NH_2-Ph Compound 107

R^{11}= 3-$NHCH_2CO_2H$-4-NH_2-Ph Compound 108

R^{11}= 2-NHCH2CO2H-4-NH_2-Ph Compound 109

R^{11}= 3-$NHCH_2CO_2H$-2-NH_2-Ph Compound 110

R^{11}= 2-$NHCH_2CO_2H$-3-NH_2-Ph Compound 111

R^{11}= 4-$(CH_2)_2CO_2H$-3-OH-Ph Compound 112

R^{11}= 4-$(CH_2)_2CO_2H$-2-OH-Ph Compound 113

R^{11}= 2-CO_2H-4-OH-Ph Compound 114

R^{11}= 2-CO_2H-3-OH-Ph Compound 115

R^{11}= 4-CO_2H-2-OH-Ph Compound 116

R^{11}= 4-CO_2H-3-OH-Ph Compound 117

R^{11}= 4-CO_2Me-Ph Compound 118

R^{11}= 3-OH-2-Naphthyl Compound 119

R^{11}= 2-NO_2-Ph Compound 120

R^{11}= 4-NO_2-Ph	Compound 121
R^{11}= 4-CF_3-Ph	Compound 122
R^{11}= 4-t-Bu-Ph	Compound 123

Compounds wherein R^8=3,4-Me_2-Ph, R^9=Me, R^{10}=Me, and R^{11} is any one of the substituents shown below.

【Hyo 3】

Table 1-3

R^{11}	Compound No.
R^{11}= 2-OH-Ph	Compound 124
R^{11}= 3-OH-Ph	Compound 125
R^{11}= 4-OH-Ph	Compound 126
R^{11}= 3,4-$(OH)_2$-Ph	Compound 127
R^{11}= 2,4-$(OH)_2$-Ph	Compound 128
R^{11}= 3,5-$(OH)_2$-Ph	Compound 129
R^{11}= 2,3-$(OH)_2$-Ph	Compound 130
R^{11}= 2,5-$(OH)_2$-Ph	Compound 131
R^{11}= 3-NO_2-Ph	Compound 132
R^{11}= 2-NH_2-Ph	Compound 133
R^{11}= 3-NH_2-Ph	Compound 134
R^{11}= 4-NH_2-Ph	Compound 135
R^{11}= 2-CO_2H-Ph	Compound 136
R^{11}= 3-CO_2H-Ph	Compound 137
R^{11}= 4-CO_2H-Ph	Compound 138

R^{11}= 2-OCH_2CO_2H-Ph Compound 139

R^{11}= 3-OCH_2CO_2H-Ph Compound 140

R^{11}= 4-OCH_2CO_2H-Ph Compound 141

R^{11}= 2-CH_2CO_2H-Ph Compound 142

R^{11}= 3-CH_2CO_2H-Ph Compound 143

R^{11}= 4-CH_2CO_2H-Ph Compound 144

R^{11}= 2-$NHCH_2CO_2H$-Ph Compound 145

R^{11}= 3-$NHCH_2CO_2H$-Ph Compound 146

R^{11}= 4-$NHCH_2CO_2H$-Ph Compound 147

R^{11}= 2-$(CH_2)_2CO_2H$-Ph Compound 148

R^{11}= 3-$(CH_2)_2CO_2H$-Ph Compound 149

R^{11}= 4-$(CH_2)_2CO_2H$-Ph Compound 150

R^{11}= 4-OCH_2CO_2H-3-OH-Ph Compound 151

R^{11}= 4-OCH_2CO_2H-2-OH-Ph Compound 152

R^{11}= 3-OCH_2CO_2H-4-OH-Ph Compound 153

R^{11}= 2-OCH_2CO_2H-4-OH-Ph Compound 154

R^{11}= 3-OCH_2CO_2H-2-OH-Ph Compound 155

R^{11}= 2-OCH_2CO_2H-3-OH-Ph Compound 156

R^{11}= 4-$NHCH_2CO_2H$-3-OH-Ph Compound 157

R^{11}= 4-$NHCH_2CO_2H$-2-OH-Ph Compound 158

R^{11}= 3-$NHCH_2CO_2H$-4-OH-Ph Compound 159

R^{11}= 2-$NHCH_2CO_2H$-4-OH-Ph Compound 160

R^{11}= 3-$NHCH_2CO_2H$-2-OH-Ph Compound 161

R^{11}= 2-$NHCH_2CO_2H$-3-OH-Ph Compound 162

R^{11}= 4-OCH_2CO_2H-3-NH_2-Ph Compound 163

R^{11}= 4-OCH_2CO_2H-2-NH_2-Ph Compound 164

R^{11}= 3-OCH_2CO_2H-4-NH_2-Ph Compound 165

R^{11}= 2-OCH_2CO_2H-4-NH_2-Ph	Compound 166
R^{11}= 3-OCH_2CO_2H-2-NH_2-Ph	Compound 167
R^{11}= 2-OCH_2CO_2H-3-NH_2-Ph	Compound 168
R^{11}= 4-$NHCH_2CO_2H$-3-NH_2-Ph	Compound 169
R^{11}= 4-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 170
R^{11}= 3-$NHCH_2CO_2H$-4-NH_2-Ph	Compound 171
R^{11}= 2-$NHCH_2CO_2H$-4-NH_2-Ph	Compound 172
R^{11}= 3-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 173
R^{11}= 2-$NHCH_2CO_2H$-3-NH_2-Ph	Compound 174
R^{11}= 4-$(CH_2)_2CO_2H$-3-OH-Ph	Compound 175
R^{11}= 4-$(CH_2)_2CO_2H$-2-OH-Ph	Compound 176
R^{11}= 2-CO_2H-4-OH-Ph	Compound 177
R^{11}= 2-CO_2H-3-OH-Ph	Compound 178
R^{11}= 4-CO_2H-2-OH-Ph	Compound 179
R^{11}= 4-CO_2H-3-OH-Ph	Compound 180
R^{11}= 4-CO_2Me-Ph	Compound 181
R^{11}= 3-OH-2-Naphthyl	Compound 182
R^{11}= 2-NO_2-Ph	Compound 183
R^{11}= 4-NO_2-Ph	Compound 184
R^{11}= 4-CF_3-Ph	Compound 185
R^{11}= 4-t-Bu-Ph	Compound 186

Compounds wherein R^8=3,4-Cl_2-Ph, R^9=Me, R^{10}=Me, and R^{11} is any one of the substituents shown below.

【Hyo 4】

Table 1-4

R^{11}	Compound No.
R^{11}= 2-OH-Ph	Compound 187
R^{11}= 3-OH-Ph	Compound 188
R^{11}= 4-OH-Ph	Compound 189
R^{11}= 3, 4-$(OH)_2$-Ph	Compound 190
R^{11}= 2, 4-$(OH)_2$-Ph	Compound 191
R^{11}= 3, 5-$(OH)_2$-Ph	Compound 192
R^{11}= 2, 3-$(OH)_2$-Ph	Compound 193
R^{11}= 2, 5-$(OH)_2$-Ph	Compound 194
R^{11}= 3-NO_2-Ph	Compound 195
R^{11}= 2-NH_2-Ph	Compound 196
R^{11}= 3-NH_2-Ph	Compound 197
R^{11}= 4-NH_2-Ph	Compound 198
R^{11}= 2-CO_2H-Ph	Compound 199
R^{11}= 3-CO_2H-Ph	Compound 200
R^{11}= 4-CO_2H-Ph	Compound 201
R^{11}= 2-OCH_2CO_2H-Ph	Compound 202
R^{11}= 3-OCH_2CO_2H-Ph	Compound 203
R^{11}= 4-OCH_2CO_2H-Ph	Compound 204
R^{11}= 2-CH_2CO_2H-Ph	Compound 205
R^{11}= 3-CH_2CO_2H-Ph	Compound 206
R^{11}= 4-CH_2CO_2H-Ph	Compound 207

R^{11}= 2-$NHCH_2CO_2H$-Ph Compound 208

R^{11}= 3-$NHCH_2CO_2H$-Ph Compound 209

R^{11}= 4-$NHCH_2CO_2H$-Ph Compound 210

R^{11}= 2-$(CH_2)_2CO_2H$-Ph Compound 211

R^{11}= 3-$(CH_2)_2CO_2H$-Ph Compound 212

R^{11}= 4-$(CH_2)_2CO_2H$-Ph Compound 213

R^{11}= 4-OCH_2CO_2H-3-OH-Ph Compound 214

R^{11}= 4-OCH_2CO_2H-2-OH-Ph Compound 215

R^{11}= 3-OCH_2CO_2H-4-OH-Ph Compound 216

R^{11}= 2-OCH_2CO_2H-4-OH-Ph Compound 217

R^{11}= 3-OCH_2CO_2H-2-OH-Ph Compound 218

R^{11}= 2-OCH_2CO_2H-3-OH-Ph Compound 219

R^{11}= 4-$NHCH_2CO_2H$-3-OH-Ph Compound 220

R^{11}= 4-$NHCH_2CO_2H$-2-OH-Ph Compound 221

R^{11}= 3-$NHCH_2CO_2H$-4-OH-Ph Compound 222

R^{11}= 2-$NHCH_2CO_2H$-4-OH-Ph Compound 223

R^{11}= 3-$NHCH_2CO_2H$-2-OH-Ph Compound 224

R^{11}= 2-$NHCH_2CO_2H$-3-OH-Ph Compound 225

R^{11}= 4-OCH_2CO_2H-3-NH_2-Ph Compound 226

R^{11}= 4-OCH_2CO_2H-2-NH_2-Ph Compound 227

R^{11}= 3-OCH_2CO_2H-4-NH_2-Ph Compound 228

R^{11}= 2-OCH_2CO_2H-4-NH_2-Ph Compound 229

R^{11}= 3-OCH_2CO_2H-2-NH_2-Ph Compound 230

R^{11}= 2-OCH_2CO_2H-3-NH_2-Ph Compound 231

R^{11}= 4-$NHCH_2CO_2H$-3-NH_2-Ph Compound 232

R^{11}= 4-$NHCH_2CO_2H$-2-NH_2-Ph Compound 233

R^{11}= 3-$NHCH_2CO_2H$-4-NH_2-Ph Compound 234

R^{11}= 2-$NHCH_2CO_2H$-4-NH_2-Ph	Compound 235
R^{11}= 3-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 236
R^{11}= 2-$NHCH_2CO_2H$-3-NH_2-Ph	Compound 237
R^{11}= 4-$(CH_2)_2CO_2H$-3-OH-Ph	Compound 238
R^{11}= 4-$(CH_2)_2CO_2H$-2-OH-Ph	Compound 239
R^{11}= 2-CO_2H-4-OH-Ph	Compound 240
R^{11}= 2-CO_2H-3-OH-Ph	Compound 241
R^{11}= 4-CO_2H-2-OH-Ph	Compound 242
R^{11}= 4-CO_2H-3-OH-Ph	Compound 243
R^{11}= 3-OH-2-Naphthyl	Compound 244
R^{11}= 2-NO_2-Ph	Compound 245
R^{11}= 4-NO_2-Ph	Compound 246
R^{11}= 4-CF_3-Ph	Compound 247
R^{11}= 4-t-Bu-Ph	Compound 248

Compounds wherein R^8=4-I-Ph, R^9=Me, R^{10}=Me, and R^{11} is any one of the substituents shown below.

【Hyo 5】

Table 1-5

R^{11}	Compound No.
R^{11}= 2-OH-Ph	Compound 249
R^{11}= 3-OH-Ph	Compound 250
R^{11}= 4-OH-Ph	Compound 251
R^{11}= 3, 4-$(OH)_2$-Ph	Compound 252
R^{11}= 2, 4-$(OH)_2$-Ph	Compound 253
R^{11}= 3, 5-$(OH)_2$-Ph	Compound 254
R^{11}= 2, 3-$(OH)_2$-Ph	Compound 255
R^{11}= 2, 5-$(OH)_2$-Ph	Compound 256
R^{11}= 3-NO_2-Ph	Compound 257
R^{11}= 2-NH_2-Ph	Compound 258
R^{11}= 3-NH_2-Ph	Compound 259
R^{11}= 4-NH_2-Ph	Compound 260
R^{11}= 2-CO_2H-Ph	Compound 261
R^{11}= 3-CO_2H-Ph	Compound 262
R^{11}= 4-CO_2H-Ph	Compound 263
R^{11}= 2-OCH_2CO_2H-Ph	Compound 264
R^{11}= 3-OCH_2CO_2H-Ph	Compound 265
R^{11}= 4-OCH_2CO_2H-Ph	Compound 266
R^{11}= 2-CH_2CO_2H-Ph	Compound 267
R^{11}= 3-CH_2CO_2H-Ph	Compound 268
R^{11}= 4-CH_2CO_2H-Ph	Compound 269

R^{11}= 2-$NHCH_2CO_2H$-Ph Compound 270

R^{11}= 3-$NHCH_2CO_2H$-Ph Compound 271

R^{11}= 4-$NHCH_2CO_2H$-Ph Compound 272

R^{11}= 2-$(CH_2)_2CO_2H$-Ph Compound 273

R^{11}= 3-$(CH_2)_2CO_2H$-Ph Compound 274

R^{11}= 4-$(CH_2)_2CO_2H$-Ph Compound 275

R^{11}= 4-OCH_2CO_2H-3-OH-Ph Compound 276

R^{11}= 4-OCH_2CO_2H-2-OH-Ph Compound 277

R^{11}= 3-OCH_2CO_2H-4-OH-Ph Compound 278

R^{11}= 2-OCH_2CO_2H-4-OH-Ph Compound 279

R^{11}= 3-OCH_2CO_2H-2-OH-Ph Compound 280

R^{11}= 2-OCH_2CO_2H-3-OH-Ph Compound 281

R^{11}= 4-$NHCH_2CO_2H$-3-OH-Ph Compound 282

R^{11}= 4-$NHCH_2CO_2H$-2-OH-Ph Compound 283

R^{11}= 3-$NHCH_2CO_2H$-4-OH-Ph Compound 284

R^{11}= 2-$NHCH_2CO_2H$-4-OH-Ph Compound 285

R^{11}= 3-$NHCH_2CO_2H$-2-OH-Ph Compound 286

R^{11}= 2-$NHCH_2CO_2H$-3-OH-Ph Compound 287

R^{11}= 4-OCH_2CO_2H-3-NH_2-Ph Compound 288

R^{11}= 4-OCH_2CO_2H-2-NH_2-Ph Compound 289

R^{11}= 3-OCH_2CO_2H-4-NH_2-Ph Compound 290

R^{11}= 2-OCH_2CO_2H-4-NH_2-Ph Compound 291

R^{11}= 3-OCH_2CO_2H-2-NH_2-Ph Compound 292

R^{11}= 2-OCH_2CO_2H-3-NH_2-Ph Compound 293

R^{11}= 4-$NHCH_2CO_2H$-3-NH_2-Ph Compound 294

R^{11}= 4-$NHCH_2CO_2H$-2-NH_2-Ph Compound 295

R^{11}= 3-$NHCH_2CO_2H$-4-NH_2-Ph Compound 296

R^{11}= 2-$NHCH_2CO_2H$-4-NH_2-Ph	Compound 297
R^{11}= 3-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 298
R^{11}= 2-$NHCH_2CO_2H$-3-NH_2-Ph	Compound 299
R^{11}= 4-$(CH_2)_2CO_2H$-3-OH-Ph	Compound 300
R^{11}= 4-$(CH_2)_2CO_2H$-2-OH-Ph	Compound 301
R^{11}= 2-CO_2H-4-OH-Ph	Compound 302
R^{11}= 2-CO_2H-3-OH-Ph	Compound 303
R^{11}= 4-CO_2H-2-OH-Ph	Compound 304
R^{11}= 4-CO_2H-3-OH-Ph	Compound 305
R^{11}= 3-OH-2-Naphthyl	Compound 306
R^{11}= 2-NO_2-Ph	Compound 307
R^{11}= 4-NO_2-Ph	Compound 308

Compounds wherein R^8=3-CF_3-Ph, R^9=Me, R^{10}=Me, and R^{11} is any one of the substituents shown below.

【Hyo 6】

Table 1-6

R^{11}	Compound No.
R^{11}= 2-OH-Ph	Compound 309
R^{11}= 3-OH-Ph	Compound 310
R^{11}= 4-OH-Ph	Compound 311
R^{11}= 3, 4-$(OH)_2$-Ph	Compound 312
R^{11}= 2, 4-$(OH)_2$-Ph	Compound 313
R^{11}= 3, 5-$(OH)_2$-Ph	Compound 314

R^{11}= 2, 3-$(OH)_2$-Ph Compound 315

R^{11}= 2, 5-$(OH)_2$-Ph Compound 316

R^{11}= 3-NO_2-Ph Compound 317

R^{11}= 2-NH_2-Ph Compound 318

R^{11}= 3-NH_2-Ph Compound 319

R^{11}= 4-NH_2-Ph Compound 320

R^{11}= 2-CO_2H-Ph Compound 321

R^{11}= 3-CO_2H-Ph Compound 322

R^{11}= 4-CO_2H-Ph Compound 323

R^{11}= 2-OCH_2CO_2H-Ph Compound 324

R^{11}= 3-OCH_2CO_2H-Ph Compound 325

R^{11}= 4-OCH_2CO_2H-Ph Compound 326

R^{11}= 2-CH_2CO_2H-Ph Compound 327

R^{11}= 3-CH_2CO_2H-Ph Compound 328

R^{11}= 4-CH_2CO_2H-Ph Compound 329

R^{11}= 2-$NHCH_2CO_2H$-Ph Compound 330

R^{11}= 3-$NHCH_2CO_2H$-Ph Compound 331

R^{11}= 4-$NHCH_2CO_2H$-Ph Compound 332

R^{11}= 2-$(CH_2)_2CO_2H$-Ph Compound 333

R^{11}= 3-$(CH_2)_2CO_2H$-Ph Compound 334

R^{11}= 4-$(CH_2)_2CO_2H$-Ph Compound 335

R^{11}= 4-OCH_2CO_2H-3-OH-Ph Compound 336

R^{11}= 4-OCH_2CO_2H-2-OH-Ph Compound 337

R^{11}= 3-OCH_2CO_2H-4-OH-Ph Compound 338

R^{11}= 2-OCH_2CO_2H-4-OH-Ph Compound 339

R^{11}= 3-OCH_2CO_2H-2-OH-Ph Compound 340

R^{11}= 2-OCH_2CO_2H-3-OH-Ph Compound 341

R^{11}= 4-$NHCH_2CO_2H$-3-OH-Ph Compound 342

R^{11}= 4-$NHCH_2CO_2H$-2-OH-Ph Compound 343

R^{11}= 3-$NHCH_2CO_2H$-4-OH-Ph Compound 344

R^{11}= 2-$NHCH_2CO_2H$-4-OH-Ph Compound 345

R^{11}= 3-$NHCH_2CO_2H$-2-OH-Ph Compound 346

R^{11}= 2-$NHCH_2CO_2H$-3-OH-Ph Compound 347

R^{11}= 4-OCH_2CO_2H-3-NH_2-Ph Compound 348

R^{11}= 4-OCH_2CO_2H-2-NH_2-Ph Compound 349

R^{11}= 3-OCH_2CO_2H-4-NH_2-Ph Compound 350

R^{11}= 2-OCH_2CO_2H-4-NH_2-Ph Compound 351

R^{11}= 3-OCH_2CO_2H-2-NH_2-Ph Compound 352

R^{11}= 2-OCH_2CO_2H-3-NH_2-Ph Compound 353

R^{11}= 4-$NHCH_2CO_2H$-3-NH_2-Ph Compound 354

R^{11}= 4-$NHCH_2CO_2H$-2-NH_2-Ph Compound 355

R^{11}= 3-$NHCH_2CO_2H$-4-NH_2-Ph Compound 356

R^{11}= 2-$NHCH_2CO_2H$-4-NH_2-Ph Compound 357

R^{11}= 3-$NHCH_2CO_2H$-2-NH_2-Ph Compound 358

R^{11}= 2-$NHCH_2CO_2H$-3-NH_2-Ph Compound 359

R^{11}= 4-$(CH_2)_2CO_2H$-3-OH-Ph Compound 360

R^{11}= 4-$(CH_2)_2CO_2H$-2-OH-Ph Compound 361

R^{11}= 2-CO_2H-4-OH-Ph Compound 362

R^{11}= 2-CO_2H-3-OH-Ph Compound 363

R^{11}= 4-CO_2H-2-OH-Ph Compound 364

R^{11}= 4-CO_2H-3-OH-Ph Compound 365

R^{11}= 4-CO_2Me-Ph Compound 366

R^{11}= 3-OH-2-Naphthyl Compound 367

R^{11}= 2-NO_2-Ph Compound 368

R^{11}= 4-NO_2-Ph	Compound 369

Compounds wherein R^8=4-CF_3-Ph, R^9=Me, R^{10}=Me, and R^{11} is any one of the substituents shown below.

【Hyo 7】

Table 1-7

R^{11}	Compound No.
R^{11}= 2-OH-Ph	Compound 370
R^{11}= 3-OH-Ph	Compound 371
R^{11}= 4-OH-Ph	Compound 372
R^{11}= 3, 4-$(OH)_2$-Ph	Compound 373
R^{11}= 2, 4-$(OH)_2$-Ph	Compound 374
R^{11}= 3, 5-$(OH)_2$-Ph	Compound 375
R^{11}= 2, 3-$(OH)_2$-Ph	Compound 376
R^{11}= 2, 5-$(OH)_2$-Ph	Compound 377
R^{11}= 3-NO_2-Ph	Compound 378
R^{11}= 2-NH_2-Ph	Compound 379
R^{11}= 3-NH_2-Ph	Compound 380
R^{11}= 4-NH_2-Ph	Compound 381
R^{11}= 2-CO_2H-Ph	Compound 382
R^{11}= 3-CO_2H-Ph	Compound 383
R^{11}= 4-CO_2H-Ph	Compound 384
R^{11}= 2-OCH_2CO_2H-Ph	Compound 385
R^{11}= 3-OCH_2CO_2H-Ph	Compound 386

R^{11}= 4-OCH_2CO_2H-Ph Compound 387

R^{11}= 2-CH_2CO_2H-Ph Compound 388

R^{11}= 3-CH_2CO_2H-Ph Compound 389

R^{11}= 4-CH_2CO_2H-Ph Compound 390

R^{11}= 2-$NHCH_2CO_2H$-Ph Compound 391

R^{11}= 3-$NHCH_2CO_2H$-Ph Compound 392

R^{11}= 4-$NHCH_2CO_2H$-Ph Compound 393

R^{11}= 2-$(CH_2)_2CO_2H$-Ph Compound 394

R^{11}= 3-$(CH_2)_2CO_2H$-Ph Compound 395

R^{11}= 4-$(CH_2)_2CO_2H$-Ph Compound 396

R^{11}= 4-OCH_2CO_2H-3-OH-Ph Compound 397

R^{11}= 4-OCH_2CO_2H-2-OH-Ph Compound 398

R^{11}= 3-OCH_2CO_2H-4-OH-Ph Compound 399

R^{11}= 2-OCH_2CO_2H-4-OH-Ph Compound 400

R^{11}= 3-OCH_2CO_2H-2-OH-Ph Compound 401

R^{11}= 2-OCH_2CO_2H-3-OH-Ph Compound 402

R^{11}= 4-$NHCH_2CO_2H$-3-OH-Ph Compound 403

R^{11}= 4-$NHCH_2CO_2H$-2-OH-Ph Compound 404

R^{11}= 3-$NHCH_2CO_2H$-4-OH-Ph Compound 405

R^{11}= 2-$NHCH_2CO_2H$-4-OH-Ph Compound 406

R^{11}= 3-$NHCH_2CO_2H$-2-OH-Ph Compound 407

R^{11}= 2-$NHCH_2CO_2H$-3-OH-Ph Compound 408

R^{11}= 4-OCH_2CO_2H-3-NH_2-Ph Compound 409

R^{11}= 4-OCH_2CO_2H-2-NH_2-Ph Compound 410

R^{11}= 3-OCH_2CO_2H-4-NH_2-Ph Compound 411

R^{11}= 2-OCH_2CO_2H-4-NH_2-Ph Compound 412

R^{11}= 3-OCH_2CO_2H-2-NH_2-Ph Compound 413

R^{11}= 2-OCH_2CO_2H-3-NH_2-Ph	Compound 414
R^{11}= 4-$NHCH_2CO_2H$-3-NH_2-Ph	Compound 415
R^{11}= 4-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 416
R^{11}= 3-$NHCH_2CO_2H$-4-NH_2-Ph	Compound 417
R^{11}= 2-$NHCH_2CO_2H$-4-NH_2-Ph	Compound 418
R^{11}= 3-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 419
R^{11}= 2-$NHCH_2CO_2H$-3-NH_2-Ph	Compound 420
R^{11}= 4-$(CH_2)_2CO_2H$-3-OH-Ph	Compound 421
R^{11}= 4-$(CH_2)_2CO_2H$-2-OH-Ph	Compound 422
R^{11}= 2-CO_2H-4-OH-Ph	Compound 423
R^{11}= 2-CO_2H-3-OH-Ph	Compound 424
R^{11}= 4-CO_2H-2-OH-Ph	Compound 425
R^{11}= 4-CO_2H-3-OH-Ph	Compound 426
R^{11}= 4-CO_2Me-Ph	Compound 427
R^{11}= 3-OH-2-Naphthyl	Compound 428
R^{11}= 2-NO_2-Ph	Compound 429
R^{11}= 4-NO_2-Ph	Compound 430

Compounds wherein R^8=4-MeNH-Ph, R^9=Me, R^{10}=Me, and R^{11} is any one of the substituents shown below.

【Hyo 8】

Table 1-8

R^{11}	Compound No.
R^{11}= 2-OH-Ph	Compound 431

R^{11}= 3-OH-Ph	Compound 432
R^{11}= 4-OH-Ph	Compound 433
R^{11}= 3, 4-$(OH)_2$-Ph	Compound 434
R^{11}= 2, 4-$(OH)_2$-Ph	Compound 435
R^{11}= 3, 5-$(OH)_2$-Ph	Compound 436
R^{11}= 2, 3-$(OH)_2$-Ph	Compound 437
R^{11}= 2, 5-$(OH)_2$-Ph	Compound 438
R^{11}= 3-NO_2-Ph	Compound 439
R^{11}= 2-NH_2-Ph	Compound 440
R^{11}= 3-NH_2-Ph	Compound 441
R^{11}= 4-NH_2-Ph	Compound 442
R^{11}= 2-CO_2H-Ph	Compound 443
R^{11}= 3-CO_2H-Ph	Compound 444
R^{11}= 4-CO_2H-Ph	Compound 445
R^{11}= 2-OCH_2CO_2H-Ph	Compound 446
R^{11}= 3-OCH_2CO_2H-Ph	Compound 447
R^{11}= 4-OCH_2CO_2H-Ph	Compound 448
R^{11}= 2-CH_2CO_2H-Ph	Compound 449
R^{11}= 3-CH_2CO_2H-Ph	Compound 450
R^{11}= 4-CH_2CO_2H-Ph	Compound 451
R^{11}= 2-$NHCH_2CO_2H$-Ph	Compound 452
R^{11}= 3-$NHCH_2CO_2H$-Ph	Compound 453
R^{11}= 4-$NHCH_2CO_2H$-Ph	Compound 454
R^{11}= 2-$(CH_2)_2CO_2H$-Ph	Compound 455
R^{11}= 3-$(CH_2)_2CO_2H$-Ph	Compound 456
R^{11}= 4-$(CH_2)_2CO_2H$-Ph	Compound 457
R^{11}= 4-OCH_2CO_2H-3-OH-Ph	Compound 458

R^{11}= 4-OCH_2CO_2H-2-OH-Ph Compound 459

R^{11}= 3-OCH_2CO_2H-4-OH-Ph Compound 460

R^{11}= 2-OCH_2CO_2H-4-OH-Ph Compound 461

R^{11}= 3-OCH_2CO_2H-2-OH-Ph Compound 462

R^{11}= 2-OCH_2CO_2H-3-OH-Ph Compound 463

R^{11}= 4-$NHCH_2CO_2H$-3-OH-Ph Compound 464

R^{11}= 4-$NHCH_2CO_2H$-2-OH-Ph Compound 465

R^{11}= 3-$NHCH_2CO_2H$-4-OH-Ph Compound 466

R^{11}=2-$NHCH_2CO_2H$-4-OH-Ph Compound 467

R^{11}= 3-$NHCH_2CO_2H$-2-OH-Ph Compound 468

R^{11}= 2-$NHCH_2CO_2H$-3-OH-Ph Compound 469

R^{11}= 4-OCH_2CO_2H-3-NH_2-Ph Compound 470

R^{11}= 4-OCH_2CO_2H-2-NH_2-Ph Compound 471

R^{11}= 3-OCH_2CO_2H-4-NH_2-Ph Compound 472

R^{11}= 2-OCH_2CO_2H-4-NH_2-Ph Compound 473

R^{11}= 3-OCH_2CO_2H-2-NH_2-Ph Compound 474

R^{11}= 2-OCH_2CO_2H-3-NH_2-Ph Compound 475

R^{11}= 4-$NHCH_2CO_2H$-3-NH_2-Ph Compound 476

R^{11}= 4-$NHCH_2CO_2H$-2-NH_2-Ph Compound 477

R^{11}= 3-$NHCH_2CO_2H$-4-NH_2-Ph Compound 478

R^{11}= 2-$NHCH_2CO_2H$-4-NH_2-Ph Compound 479

R^{11}= 3-$NHCH_2CO_2H$-2-NH_2-Ph Compound 480

R^{11}= 2-$NHCH_2CO_2H$-3-NH_2-Ph Compound 481

R^{11}= 4-$(CH_2)_2CO_2H$-3-OH-Ph Compound 482

R^{11}= 4-$(CH_2)_2CO_2H$-2-OH-Ph Compound 483

R^{11}= 2-CO_2H-4-OH-Ph Compound 484

R^{11}= 2-CO_2H-3-OH-Ph Compound 485

R^{11}= 4-CO_2H-2-OH-Ph	Compound 486
R^{11}= 4-CO_2H-3-OH-Ph	Compound 487

Compounds wherein R^8=4-EtNH-Ph, R^9=Me, R^{10}=Me, and R^{11} is any one of the substituents shown below.

【Hyo 9】

Table 1-9

R^{11}	Compound No.
R^{11}= 2-OH-Ph	Compound 488
R^{11}= 3-OH-Ph	Compound 489
R^{11}= 4-OH-Ph	Compound 490
R^{11}= 3, 4-$(OH)_2$-Ph	Compound 491
R^{11}= 2, 4-$(OH)_2$-Ph	Compound 492
R^{11}= 3, 5-$(OH)_2$-Ph	Compound 493
R^{11}= 2, 3-$(OH)_2$-Ph	Compound 494
R^{11}= 2, 5-$(OH)_2$-Ph	Compound 495
R^{11}= 3-NO_2-Ph	Compound 496
R^{11}= 2-NH_2-Ph	Compound 497
R^{11}= 3-NH_2-Ph	Compound 498
R^{11}= 4-NH_2-Ph	Compound 499
R^{11}= 2-CO_2H-Ph	Compound 500
R^{11}= 3-CO_2H-Ph	Compound 501
R^{11}= 4-CO_2H-Ph	Compound 502
R^{11}= 2-OCH_2CO_2H-Ph	Compound 503

R^{11}= 3-OCH_2CO_2H-Ph Compound 504

R^{11}= 4-OCH_2CO_2H-Ph Compound 505

R^{11}= 2-CH_2CO_2H-Ph Compound 506

R^{11}= 3-CH_2CO_2H-Ph Compound 507

R^{11}= 4-CH_2CO_2H-Ph Compound 508

R^{11}= 2-$NHCH_2CO_2H$-Ph Compound 509

R^{11}= 3-$NHCH_2CO_2H$-Ph Compound 510

R^{11}= 4-$NHCH_2CO_2H$-Ph Compound 511

R^{11}= 2-$(CH_2)_2CO_2H$-Ph Compound 512

R^{11}= 3-$(CH_2)_2CO_2H$-Ph Compound 513

R^{11}= 4-$(CH_2)_2CO_2H$-Ph Compound 514

R^{11}= 4-OCH_2CO_2H-3-OH-Ph Compound 515

R^{11}= 4-OCH_2CO_2H-2-OH-Ph Compound 516

R^{11}= 3-OCH_2CO_2H-4-OH-Ph Compound 517

R^{11}= 2-OCH_2CO_2H-4-OH-Ph Compound 518

R^{11}= 3-OCH_2CO_2H-2-OH-Ph Compound 519

R^{11}= 2-OCH_2CO_2H-3-OH-Ph Compound 520

R^{11}= 4-$NHCH_2CO_2H$-3-OH-Ph Compound 521

R^{11}= 4-$NHCH_2CO_2H$-2-OH-Ph Compound 522

R^{11}= 3-$NHCH_2CO_2H$-4-OH-Ph Compound 523

R^{11}= 2-$NHCH_2CO_2H$-4-OH-Ph Compound 524

R^{11}= 3-$NHCH_2CO_2H$-2-OH-Ph Compound 525

R^{11}= 2-$NHCH_2CO_2H$-3-OH-Ph Compound 526

R^{11}= 4-OCH_2CO_2H-3-NH_2-Ph Compound 527

R^{11}= 4-OCH_2CO_2H-2-NH_2-Ph Compound 528

R^{11}= 3-OCH_2CO_2H-4-NH_2-Ph Compound 529

R^{11}= 2-OCH_2CO_2H-4-NH_2-Ph Compound 530

R^{11}= 3-OCH_2CO_2H-2-NH_2-Ph	Compound 531
R^{11}= 2-OCH_2CO_2H-3-NH_2-Ph	Compound 532
R^{11}= 4-$NHCH_2CO_2H$-3-NH_2-Ph	Compound 533
R^{11}= 4-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 534
R^{11}=3-$NHCH_2CO_2H$-4-NH_2-Ph	Compound 535
R^{11}= 2-$NHCH_2CO_2H$-4-NH_2-Ph	Compound 536
R^{11}= 3-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 537
R^{11}= 2-$NHCH_2CO_2H$-3-NH_2-Ph	Compound 538
R^{11}= 4-$(CH_2)_2CO_2H$-3-OH-Ph	Compound 539
R^{11}= 4-$(CH_2)_2CO_2H$-2-OH-Ph	Compound 540
R^{11}= 2-CO_2H-4-OH-Ph	Compound 541
R^{11}= 2-CO_2H-3-OH-Ph	Compound 542
R^{11}= 4-CO_2H-2-OH-Ph	Compound 543
R^{11}= 4-CO_2H-3-OH-Ph	Compound 544

Compounds wherein R^8=4-Me_2N-Ph, R^9=Me, R^{10}=Me, and R^{11} is any one of the substituents shown below.

【Hyo 10】

Table 1-10

R^{11}	Compound No.
R^{11}= 2-OH-Ph	Compound 545
R^{11}= 3-OH-Ph	Compound 546
R^{11}= 4-OH-Ph	Compound 547
R^{11}= 3, 4-$(OH)_2$-Ph	Compound 548

R^{11}= 2, 4-$(OH)_2$-Ph Compound 549

R^{11}= 3, 5-$(OH)_2$-Ph Compound 550

R^{11}= 2, 3-$(OH)_2$-Ph Compound 551

R^{11}= 2, 5-$(OH)_2$-Ph Compound 552

R^{11}= 3-NO_2-Ph Compound 553

R^{11}= 2-NH_2-Ph Compound 554

R^{11}= 3-NH_2-Ph Compound 555

R^{11}= 4-NH_2-Ph Compound 556

R^{11}= 2-CO_2H-Ph Compound 557

R^{11}= 3-CO_2H-Ph Compound 558

R^{11}= 4-CO_2H-Ph Compound 559

R^{11}= 2-OCH_2CO_2H-Ph Compound 560

R^{11}= 3-OCH_2CO_2H-Ph Compound 561

R^{11}= 4-OCH_2CO_2H-Ph Compound 562

R^{11}= 2-CH_2CO_2H-Ph Compound 563

R^{11}= 3-CH_2CO_2H-Ph Compound 564

R^{11}= 4-CH_2CO_2H-Ph Compound 565

R^{11}= 2-$NHCH_2CO_2H$-Ph Compound 566

R^{11}= 3-$NHCH_2CO_2H$-Ph Compound 567

R^{11}= 4-$NHCH_2CO_2H$-Ph Compound 568

R^{11}= 2-$(CH_2)_2CO_2H$-Ph Compound 569

R^{11}= 3-$(CH_2)_2CO_2H$-Ph Compound 570

R^{11}= 4-$(CH_2)_2CO_2H$-Ph Compound 571

R^{11}= 4-OCH_2CO_2H-3-OH-Ph Compound 572

R^{11}= 4-OCH_2CO_2H-2-OH-Ph Compound 573

R^{11}= 3-OCH_2CO_2H-4-OH-Ph Compound 574

R^{11}= 2-OCH_2CO_2H-4-OH-Ph Compound 575

R^{11}= 3-OCH_2CO_2H-2-OH-Ph	Compound 576
R^{11}= 2-OCH_2CO_2H-3-OH-Ph	Compound 577
R^{11}= 4-$NHCH_2CO_2H$-3-OH-Ph	Compound 578
R^{11}= 4-$NHCH_2CO_2H$-2-OH-Ph	Compound 579
R^{11}= 3-$NHCH_2CO_2H$-4-OH-Ph	Compound 580
R^{11}= 2-$NHCH_2CO_2H$-4-OH-Ph	Compound 581
R^{11}= 3-$NHCH_2CO_2H$-2-OH-Ph	Compound 582
R^{11}= 2-$NHCH_2CO_2H$-3-OH-Ph	Compound 583
R^{11}= 4-OCH_2CO_2H-3-NH_2-Ph	Compound 584
R^{11}= 4-OCH_2CO_2H-2-NH_2-Ph	Compound 585
R^{11}= 3-OCH_2CO_2H-4-NH_2-Ph	Compound 586
R^{11}= 2-OCH_2CO_2H-4-NH_2-Ph	Compound 587
R^{11}= 3-OCH_2CO_2H-2-NH_2-Ph	Compound 588
R^{11}= 2-OCH_2CO_2H-3-NH_2-Ph	Compound 589
R^{11}= 4-$NHCH_2CO_2H$-3-NH_2-Ph	Compound 590
R^{11}= 4-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 591
R^{11}= 3-$NHCH_2CO_2H$-4-NH_2-Ph	Compound 592
R^{11}= 2-$NHCH_2CO_2H$-4-NH_2-Ph	Compound 593
R^{11}= 3-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 594
R^{11}= 2-$NHCH_2CO_2H$-3-NH_2-Ph	Compound 595
R^{11}= 4-$(CH_2)_2CO_2H$-3-OH-Ph	Compound 596
R^{11}= 4-$(CH_2)_2CO_2H$-2-OH-Ph	Compound 597
R^{11}= 2-CO_2H-4-OH-Ph	Compound 598
R^{11}= 2-CO_2H-3-OH-Ph	Compound 599
R^{11}= 4-CO_2H-2-OH-Ph	Compound 600
R^{11}= 4-CO_2H-3-OH-Ph	Compound 601

Compounds wherein R^8=4-Et_2N-Ph, R^9=Me, R^{10}=Me, and R^{11} is any one of the substituents shown below.

【Hyo 11】

Table 1-11

R^{11}	Compound No.
R^{11}= 2-OH-Ph	Compound 602
R^{11}= 3-OH-Ph	Compound 603
R^{11}= 4-OH-Ph	Compound 604
R^{11}= 3, 4-$(OH)_2$-Ph	Compound 605
R^{11}= 2, 4-$(OH)_2$-Ph	Compound 606
R^{11}= 3, 5-$(OH)_2$-Ph	Compound 607
R^{11}= 2, 3-$(OH)_2$-Ph	Compound 608
R^{11}= 2, 5-$(OH)_2$-Ph	Compound 609
R^{11}= 3-NO_2-Ph	Compound 610
R^{11}= 2-NH_2-Ph	Compound 611
R^{11}= 3-NH_2-Ph	Compound 612
R^{11}= 4-NH_2-Ph	Compound 613
R^{11}= 2-CO_2H-Ph	Compound 614
R^{11}= 3-CO_2H-Ph	Compound 615
R^{11}= 4-CO_2H-Ph	Compound 616
R^{11}= 2-OCH_2CO_2H-Ph	Compound 617
R^{11}= 3-OCH_2CO_2H-Ph	Compound 618
R^{11}= 4-OCH_2CO_2H-Ph	Compound 619
R^{11}= 2-CH_2CO_2H-Ph	Compound 620

R^{11}= 3-CH_2CO_2H-Ph Compound 621

R^{11}= 4-CH_2CO_2H-Ph Compound 622

R^{11}= 2-$NHCH_2CO_2H$-Ph Compound 623

R^{11}= 3-$NHCH_2CO_2H$-Ph Compound 624

R^{11}= 4-$NHCH_2CO_2H$-Ph Compound 625

R^{11}= 2-$(CH_2)_2CO_2H$-Ph Compound 626

R^{11}= 3-$(CH_2)_2CO_2H$-Ph Compound 627

R^{11}= 4-$(CH_2)_2CO_2H$-Ph Compound 628

R^{11}= 4-OCH_2CO_2H-3-OH-Ph Compound 629

R^{11}= 4-OCH_2CO_2H-2-OH-Ph Compound 630

R^{11}= 3-OCH_2CO_2H-4-OH-Ph Compound 631

R^{11}= 2-OCH_2CO_2H-4-OH-Ph Compound 632

R^{11}= 3-OCH_2CO_2H-2-OH-Ph Compound 633

R^{11}= 2-OCH_2CO_2H-3-OH-Ph Compound 634

R^{11}= 4-$NHCH_2CO_2H$-3-OH-Ph Compound 635

R^{11}= 4-$NHCH_2CO_2H$-2-OH-Ph Compound 636

R^{11}= 3-$NHCH_2CO_2H$-4-OH-Ph Compound 637

R^{11}= 2-$NHCH_2CO_2H$-4-OH-Ph Compound 638

R^{11}= 3-$NHCH_2CO_2H$-2-OH-Ph Compound 639

R^{11}= 2-$NHCH_2CO_2H$-3-OH-Ph Compound 640

R^{11}= 4-OCH_2CO_2H-3-NH_2-Ph Compound 641

R^{11}= 4-OCH_2CO_2H-2-NH_2-Ph Compound 642

R^{11}= 3-OCH_2CO_2H-4-NH_2-Ph Compound 643

R^{11}= 2-OCH_2CO_2H-4-NH_2-Ph Compound 644

R^{11}= 3-OCH_2CO_2H-2-NH_2-Ph Compound 645

R^{11}= 2-OCH_2CO_2H-3-NH_2-Ph Compound 646

R^{11}= 4-$NHCH_2CO_2H$-3-NH_2-Ph Compound 647

R^{11}= 4-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 648
R^{11}= 3-$NHCH_2CO_2H$-4-NH_2-Ph	Compound 649
R^{11}= 2-$NHCH_2CO_2H$-4-NH_2-Ph	Compound 650
R^{11}= 3-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 651
R^{11}= 2-$NHCH_2CO_2H$-3-NH_2-Ph	Compound 652
R^{11}= 4-$(CH_2)_2CO_2H$-3-OH-Ph	Compound 653
R^{11}= 4-$(CH_2)_2CO_2H$-2-OH-Ph	Compound 654
R^{11}= 2-CO_2H-4-OH-Ph	Compound 655
R^{11}= 2-CO_2H-3-OH-Ph	Compound 656
R^{11}= 4-CO_2H-2-OH-Ph	Compound 657
R^{11}= 4-CO_2H-3-OH-Ph	Compound 658

Compounds wherein R^8=4-MeO-Ph, R^9=Me, R^{10}=Me, and R^{11} is any one of the substituents shown below.

【Hyo 12】

Table 1-12

R^{11}	Compound No.
R^{11}= 2-OH-Ph	Compound 659
R^{11}= 3-OH-Ph	Compound 660
R^{11}= 4-OH-Ph	Compound 661
R^{11}= 3, 4-$(OH)_2$-Ph	Compound 662
R^{11}= 2, 4-$(OH)_2$-Ph	Compound 663
R^{11}= 3, 5-$(OH)_2$-Ph	Compound 664
R^{11}= 2, 3-$(OH)_2$-Ph	Compound 665

R^{11}= 2,5-$(OH)_2$-Ph Compound 666

R^{11}= 3-NO_2-Ph Compound 667

R^{11}= 2-NH_2-Ph Compound 668

R^{11}= 3-NH_2-Ph Compound 669

R^{11}= 4-NH_2-Ph Compound 670

R^{11}= 2-CO_2H-Ph Compound 671

R^{11}= 3-CO_2H-Ph Compound 672

R^{11}= 4-CO_2H-Ph Compound 673

R^{11}= 2-OCH_2CO_2H-Ph Compound 674

R^{11}= 3-OCH_2CO_2H-Ph Compound 675

R^{11}= 4-OCH_2CO_2H-Ph Compound 676

R^{11}= 2-CH_2CO_2H-Ph Compound 677

R^{11}= 3-CH_2CO_2H-Ph Compound 678

R^{11}= 4-CH_2CO_2H-Ph Compound 679

R^{11}= 2-$NHCH_2CO_2H$-Ph Compound 680

R^{11}= 3-$NHCH_2CO_2H$-Ph Compound 681

R^{11}= 4-$NHCH_2CO_2H$-Ph Compound 682

R^{11}= 2-$(CH_2)_2CO_2H$-Ph Compound 683

R^{11}= 3-$(CH_2)_2CO_2H$-Ph Compound 684

R^{11}= 4-$(CH_2)_2CO_2H$-Ph Compound 685

R^{11}= 4-OCH_2CO_2H-3-OH-Ph Compound 686

R^{11}= 4-OCH_2CO_2H-2-OH-Ph Compound 687

R^{11}= 3-OCH_2CO_2H-4-OH-Ph Compound 688

R^{11}= 2-OCH_2CO_2H-4-OH-Ph Compound 689

R^{11}= 3-OCH_2CO_2H-2-OH-Ph Compound 690

R^{11}= 2-OCH_2CO_2H-3-OH-Ph Compound 691

R^{11}= 4-$NHCH_2CO_2H$-3-OH-Ph Compound 692

R^{11}= 4-$NHCH_2CO_2H$-2-OH-Ph	Compound 693
R^{11}= 3-$NHCH_2CO_2H$-4-OH-Ph	Compound 694
R^{11}= 2-$NHCH_2CO_2H$-4-OH-Ph	Compound 695
R^{11}= 3-$NHCH_2CO_2H$-2-OH-Ph	Compound 696
R^{11}= 2-$NHCH_2CO_2H$-3-OH-Ph	Compound 697
R^{11}= 4-OCH_2CO_2H-3-NH_2-Ph	Compound 698
R^{11}= 4-OCH_2CO_2H-2-NH_2-Ph	Compound 699
R^{11}= 3-OCH_2CO_2H-4-NH_2-Ph	Compound 700
R^{11}= 2-OCH_2CO_2H-4-NH_2-Ph	Compound 701
R^{11}= 3-OCH_2CO_2H-2-NH_2-Ph	Compound 702
R^{11}= 2-OCH_2CO_2H-3-NH_2-Ph	Compound 703
R^{11}= 4-$NHCH_2CO_2H$-3-NH_2-Ph	Compound 704
R^{11}= 4-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 705
R^{11}= 3-$NHCH_2CO_2H$-4-NH_2-Ph	Compound 706
R^{11}= 2-$NHCH_2CO_2H$-4-NH_2-Ph	Compound 707
R^{11}= 3-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 708
R^{11}= 2-$NHCH_2CO_2H$-3-NH_2-Ph	Compound 709
R^{11}= 4-$(CH_2)_2CO_2H$-3-OH-Ph	Compound 710
R^{11}= 4-$(CH_2)_2CO_2H$-2-OH-Ph	Compound 711
R^{11}= 2-CO_2H-4-OH-Ph	Compound 712
R^{11}= 2-CO_2H-3-OH-Ph	Compound 713
R^{11}= 4-CO_2H-2-OH-Ph	Compound 714
R^{11}= 4-CO_2H-3-OH-Ph	Compound 715

Compounds wherein R^8=4-EtO-Ph, R^9=Me, R^{10}=Me, and R^{11} is any one of the substituents shown below.

【Hyo 13】

Table 1-13

R^{11}	Compound No.
R^{11}= 2-OH-Ph	Compound 716
R^{11}= 3-OH-Ph	Compound 717
R^{11}= 4-OH-Ph	Compound 718
R^{11}= 3, 4-$(OH)_2$-Ph	Compound 719
R^{11}= 2, 4-$(OH)_2$-Ph	Compound 720
R^{11}= 3, 5-$(OH)_2$-Ph	Compound 721
R^{11}= 2, 3-$(OH)_2$-Ph	Compound 722
R^{11}= 2, 5-$(OH)_2$-Ph	Compound 723
R^{11}= 3-NO_2-Ph	Compound 724
R^{11}= 2-NH_2-Ph	Compound 725
R^{11}= 3-NH_2-Ph	Compound 726
R^{11}= 4-NH_2-Ph	Compound 727
R^{11}= 2-CO_2H-Ph	Compound 728
R^{11}= 3-CO_2H-Ph	Compound 729
R^{11}= 4-CO_2H-Ph	Compound 730
R^{11}= 2-OCH_2CO_2H-Ph	Compound 731
R^{11}= 3-OCH_2CO_2H-Ph	Compound 732
R^{11}= 4-OCH_2CO_2H-Ph	Compound 733
R^{11}= 2-CH_2CO_2H-Ph	Compound 734
R^{11}= 3-CH_2CO_2H-Ph	Compound 735
R^{11}= 4-CH_2CO_2H-Ph	Compound 736

R^{11}= 2-$NHCH_2CO_2H$-Ph Compound 737

R^{11}= 3-$NHCH_2CO_2H$-Ph Compound 738

R^{11}= 4-$NHCH_2CO_2H$-Ph Compound 739

R^{11}= 2-$(CH_2)_2CO_2H$-Ph Compound 740

R^{11}= 3-$(CH_2)_2CO_2H$-Ph Compound 741

R^{11}= 4-$(CH_2)_2CO_2H$-Ph Compound 742

R^{11}= 4-OCH_2CO_2H-3-OH-Ph Compound 743

R^{11}= 4-OCH_2CO_2H-2-OH-Ph Compound 744

R^{11}= 3-OCH_2CO_2H-4-OH-Ph Compound 745

R^{11}= 2-OCH_2CO_2H-4-OH-Ph Compound 746

R^{11}= 3-OCH_2CO_2H-2-OH-Ph Compound 747

R^{11}= 2-OCH_2CO_2H-3-OH-Ph Compound 748

R^{11}= 4-$NHCH_2CO_2H$-3-OH-Ph Compound 749

R^{11}= 4-$NHCH_2CO_2H$-2-OH-Ph Compound 750

R^{11}= 3-$NHCH_2CO_2H$-4-OH-Ph Compound 751

R^{11}= 2-$NHCH_2CO_2H$-4-OH-Ph Compound 752

R^{11}= 3-$NHCH_2CO_2H$-2-OH-Ph Compound 753

R^{11}= 2-$NHCH_2CO_2H$-3-OH-Ph Compound 754

R^{11}= 4-OCH_2CO_2H-3-NH_2-Ph Compound 755

R^{11}= 4-OCH_2CO_2H-2-NH_2-Ph Compound 756

R^{11}= 3-OCH_2CO_2H-4-NH_2-Ph Compound 757

R^{11}= 2-OCH_2CO_2H-4-NH_2-Ph Compound 758

R^{11}= 3-OCH_2CO_2H-2-NH_2-Ph Compound 759

R^{11}= 2-OCH_2CO_2H-3-NH_2-Ph Compound 760

R^{11}= 4-$NHCH_2CO_2H$-3-NH_2-Ph Compound 761

R^{11}= 4-$NHCH_2CO_2H$-2-NH_2-Ph Compound 762

R^{11}= 3-$NHCH_2CO_2H$-4-NH_2-Ph Compound 763

R^{11}= 2-$NHCH_2CO_2H$-4-NH_2-Ph	Compound 764
R^{11}= 3-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 765
R^{11}= 2-$NHCH_2CO_2H$-3-NH_2-Ph	Compound 766
R^{11}= 4-$(CH_2)_2CO_2H$-3-OH-Ph	Compound 767
R^{11}= 4-$(CH_2)_2CO_2H$-2-OH-Ph	Compound 768
R^{11}= 2-CO_2H-4-OH-Ph	Compound 769
R^{11}= 2-CO_2H-3-OH-Ph	Compound 770
R^{11}= 4-CO_2H-2-OH-Ph	Compound 771
R^{11}= 4-CO_2H-3-OH-Ph	Compound 772

Compounds wherein R^8=4-n-PrO-Ph, R^9=Me, R^{10}=Me, and R^{11} is any one of the substituents shown below.

【Hyo 1.4】

Table 1-14

R^{11}	Compound No.
R^{11}= 2-OH-Ph	Compound 773
R^{11}= 3-OH-Ph	Compound 774
R^{11}= 4-OH-Ph	Compound 775
R^{11}= 3, 4-$(OH)_2$-Ph	Compound 776
R^{11}= 2, 4-$(OH)_2$-Ph	Compound 777
R^{11}= 3, 5-$(OH)_2$-Ph	Compound 778
R^{11}= 2, 3-$(OH)_2$-Ph	Compound 779
R^{11}= 2, 5-$(OH)_2$-Ph	Compound 780
R^{11}= 3-NO_2-Ph	Compound 781

R^{11}= 2-NH_2-Ph Compound 782

R^{11}= 3-NH_2-Ph Compound 783

R^{11}= 4-NH_2-Ph Compound 784

R^{11}= 2-CO_2H-Ph Compound 785

R^{11}= 3-CO_2H-Ph Compound 786

R^{11}= 4-CO_2H-Ph Compound 787

R^{11}= 2-OCH_2CO_2H-Ph Compound 788

R^{11}= 3-OCH_2CO_2H-Ph Compound 789

R^{11}= 4-OCH_2CO_2H-Ph Compound 790

R^{11}= 2-CH_2CO_2H-Ph Compound 791

R^{11}= 3-CH_2CO_2H-Ph Compound 792

R^{11}= 4-CH_2CO_2H-Ph Compound 793

R^{11}= 2-$NHCH_2CO_2H$-Ph Compound 794

R^{11}= 3-$NHCH_2CO_2H$-Ph Compound 795

R^{11}= 4-$NHCH_2CO_2H$-Ph Compound 796

R^{11}= 2-$(CH_2)_2CO_2H$-Ph Compound 797

R^{11}= 3-$(CH_2)_2CO_2H$-Ph Compound 798

R^{11}= 4-$(CH_2)_2CO_2H$-Ph Compound 799

R^{11}= 4-OCH_2CO_2H-3-OH-Ph Compound 800

R^{11}= 4-OCH_2CO_2H-2-OH-Ph Compound 801

R^{11}= 3-OCH_2CO_2H-4-OH-Ph Compound 802

R^{11}= 2-OCH_2CO_2H-4-OH-Ph Compound 803

R^{11}= 3-OCH_2CO_2H-2-OH-Ph Compound 804

R^{11}= 2-OCH_2CO_2H-3-OH-Ph Compound 805

R^{11}= 4-$NHCH_2CO_2H$-3-OH-Ph Compound 806

R^{11}= 4-$NHCH_2CO_2H$-2-OH-Ph Compound 807

R^{11}= 3-$NHCH_2CO_2H$-4-OH-Ph Compound 808

R^{11}= 2-$NHCH_2CO_2H$-4-OH-Ph	Compound 809
R^{11}= 3-$NHCH_2CO_2H$-2-OH-Ph	Compound 810
R^{11}= 2-$NHCH_2CO_2H$-3-OH-Ph	Compound 811
R^{11}= 4-OCH_2CO_2H-3-NH_2-Ph	Compound 812
R^{11}= 4-OCH_2CO_2H-2-NH_2-Ph	Compound 813
R^{11}= 3-OCH_2CO_2H-4-NH_2-Ph	Compound 814
R^{11}= 2-OCH_2CO_2H-4-NH_2-Ph	Compound 815
R^{11}= 3-OCH_2CO_2H-2-NH_2-Ph	Compound 816
R^{11}= 2-OCH_2CO_2H-3-NH_2-Ph	Compound 817
R^{11}= 4-$NHCH_2CO_2H$-3-NH_2-Ph	Compound 818
R^{11}= 4-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 819
R^{11}= 3-$NHCH_2CO_2H$-4-NH_2-Ph	Compound 820
R^{11}= 2-NHCH2CO2H-4-NH_2-Ph	Compound 821
R^{11}= 3-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 822
R^{11}= 2-$NHCH_2CO_2H$-3-NH_2-Ph	Compound 823
R^{11}= 4-$(CH_2)_2CO_2H$-3-OH-Ph	Compound 824
R^{11}= 4-$(CH_2)_2CO_2H$-2-OH-Ph	Compound 825
R^{11}= 2-CO_2H-4-OH-Ph	Compound 826
R^{11}= 2-CO_2H-3-OH-Ph	Compound 827
R^{11}= 4-CO_2H-2-OH-Ph	Compound 828
R^{11}= 4-CO_2H-3-OH-Ph	Compound 829

Compounds wherein R^8=4-i-PrO-Ph, R^9=Me, R^{10}=Me, and R^{11} is any one of the substituents shown below.

【Hyo 15】

Table 1-15

R^{11}	Compound No.
R^{11}= 2-OH-Ph	Compound 830
R^{11}= 3-OH-Ph	Compound 831
R^{11}= 4-OH-Ph	Compound 832
R^{11}= 3, 4-$(OH)_2$-Ph	Compound 833
R^{11}= 2, 4-$(OH)_2$-Ph	Compound 834
R^{11}= 3, 5-$(OH)_2$-Ph	Compound 835
R^{11}= 2, 3-$(OH)_2$-Ph	Compound 836
R^{11}= 2, 5-$(OH)_2$-Ph	Compound 837
R^{11}= 3-NO_2-Ph	Compound 838
R^{11}= 2-NH_2-Ph	Compound 839
R^{11}= 3-NH_2-Ph	Compound 840
R^{11}= 4-NH_2-Ph	Compound 841
R^{11}= 2-CO_2H-Ph	Compound 842
R^{11}= 3-CO_2H-Ph	Compound 843
R^{11}= 4-CO_2H-Ph	Compound 844
R^{11}= 2-OCH_2CO_2H-Ph	Compound 845
R^{11}= 3-OCH_2CO_2H-Ph	Compound 846
R^{11}= 4-OCH_2CO_2H-Ph	Compound 847
R^{11}= 2-CH_2CO_2H-Ph	Compound 848
R^{11}= 3-CH_2CO_2H-Ph	Compound 849
R^{11}= 4-CH_2CO_2H-Ph	Compound 850

R^{11}= 2-$NHCH_2CO_2H$-Ph Compound 851

R^{11}= 3-$NHCH_2CO_2H$-Ph Compound 852

R^{11}= 4-$NHCH_2CO_2H$-Ph Compound 853

R^{11}= 2-$(CH_2)_2CO_2H$-Ph Compound 854

R^{11}= 3-$(CH_2)_2CO_2H$-Ph Compound 855

R^{11}= 4-$(CH_2)_2CO_2H$-Ph Compound 856

R^{11}= 4-OCH_2CO_2H-3-OH-Ph Compound 857

R^{11}= 4-OCH_2CO_2H-2-OH-Ph Compound 858

R^{11}= 3-OCH_2CO_2H-4-OH-Ph Compound 859

R^{11}= 2-OCH_2CO_2H-4-OH-Ph Compound 860

R^{11}= 3-OCH_2CO_2H-2-OH-Ph Compound 861

R^{11}= 2-OCH_2CO_2H-3-OH-Ph Compound 862

R^{11}= 4-$NHCH_2CO_2H$-3-OH-Ph Compound 863

R^{11}= 4-$NHCH_2CO_2H$-2-OH-Ph Compound 864

R^{11}= 3-$NHCH_2CO_2H$-4-OH-Ph Compound 865

R^{11}= 2-$NHCH_2CO_2H$-4-OH-Ph Compound 866

R^{11}= 3-$NHCH_2CO_2H$-2-OH-Ph Compound 867

R^{11}= 2-$NHCH_2CO_2H$-3-OH-Ph Compound 868

R^{11}= 4-OCH_2CO_2H-3-NH_2-Ph Compound 869

R^{11}= 4-OCH_2CO_2H-2-NH_2-Ph Compound 870

R^{11}= 3-OCH_2CO_2H-4-NH_2-Ph Compound 871

R^{11}= 2-OCH_2CO_2H-4-NH_2-Ph Compound 872

R^{11}= 3-OCH_2CO_2H-2-NH_2-Ph Compound 873

R^{11}= 2-OCH_2CO_2H-3-NH_2-Ph Compound 874

R^{11}= 4-$NHCH_2CO_2H$-3-NH_2-Ph Compound 875

R^{11}= 4-$NHCH_2CO_2H$-2-NH_2-Ph Compound 876

R^{11}= 3-$NHCH_2CO_2H$-4-NH_2-Ph Compound 877

R^{11}= 2-$NHCH_2CO_2H$-4-NH_2-Ph	Compound 878
R^{11}= 3-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 879
R^{11}= 2-$NHCH_2CO_2H$-3-NH_2-Ph	Compound 880
R^{11}= 4-$(CH_2)_2CO_2H$-3-OH-Ph	Compound 881
R^{11}= 4-$(CH_2)_2CO_2H$-2-OH-Ph	Compound 882
R^{11}= 2-CO_2H-4-OH-Ph	Compound 883
R^{11}= 2-CO_2H-3-OH-Ph	Compound 884
R^{11}= 4-CO_2H-2-OH-Ph	Compound 885
R^{11}= 4-CO_2H-3-OH-Ph	Compound 886

Compounds wherein R^8=4-t-BuO-Ph, R^9=Me, R^{10}=Me, and R^{11} is any one of the substituents shown below.

【Hyo 16】

Table 1-16

R^{11}	Compound No.
R^{11}= 2-OH-Ph	Compound 887
R^{11}= 3-OH-Ph	Compound 888
R^{11}= 4-OH-Ph	Compound 889
R^{11}= 3, 4-$(OH)_2$-Ph	Compound 890
R^{11}= 2, 4-$(OH)_2$-Ph	Compound 891
R^{11}= 3, 5-$(OH)_2$-Ph	Compound 892
R^{11}= 2, 3-$(OH)_2$-Ph	Compound 893
R^{11}= 2, 5-$(OH)_2$-Ph	Compound 894
R^{11}= 3-NO_2-Ph	Compound 895

R^{11}= 2-NH_2-Ph	Compound 896
R^{11}= 3-NH_2-Ph	Compound 897
R^{11}= 4-NH_2-Ph	Compound 898
R^{11}= 2-CO_2H-Ph	Compound 899
R^{11}= 3-CO_2H-Ph	Compound 900
R^{11}= 4-CO_2H-Ph	Compound 901
R^{11}= 2-OCH_2CO_2H-Ph	Compound 902
R^{11}= 3-OCH_2CO_2H-Ph	Compound 903
R^{11}= 4-OCH_2CO_2H-Ph	Compound 904
R^{11}= 2-CH_2CO_2H-Ph	Compound 905
R^{11}= 3-CH_2CO_2H-Ph	Compound 906
R^{11}= 4-CH_2CO_2H-Ph	Compound 907
R^{11}= 2-$NHCH_2CO_2H$-Ph	Compound 908
R^{11}= 3-$NHCH_2CO_2H$-Ph	Compound 909
R^{11}= 4-$NHCH_2CO_2H$-Ph	Compound 910
R^{11}= 2-$(CH_2)_2CO_2H$-Ph	Compound 911
R^{11}= 3-$(CH_2)_2CO_2H$-Ph	Compound 912
R^{11}= 4-$(CH_2)_2CO_2H$-Ph	Compound 913
R^{11}= 4-OCH_2CO_2H-3-OH-Ph	Compound 914
R^{11}= 4-OCH_2CO_2H-2-OH-Ph	Compound 915
R^{11}= 3-OCH_2CO_2H-4-OH-Ph	Compound 916
R^{11}= 2-OCH_2CO_2H-4-OH-Ph	Compound 917
R^{11}= 3-OCH_2CO_2H-2-OH-Ph	Compound 918
R^{11}= 2-OCH_2CO_2H-3-OH-Ph	Compound 919
R^{11}= 4-$NHCH_2CO_2H$-3-OH-Ph	Compound 920
R^{11}= 4-$NHCH_2CO_2H$-2-OH-Ph	Compound 921
R^{11}= 3-$NHCH_2CO_2H$-4-OH-Ph	Compound 922

R^{11}= 2-$NHCH_2CO_2H$-4-OH-Ph	Compound 923
R^{11}= 3-$NHCH_2CO_2H$-2-OH-Ph	Compound 924
R^{11}= 2-$NHCH_2CO_2H$-3-OH-Ph	Compound 925
R^{11}= 4-OCH_2CO_2H-3-NH_2-Ph	Compound 926
R^{11}= 4-OCH_2CO_2H-2-NH_2-Ph	Compound 927
R^{11}= 3-OCH_2CO_2H-4-NH_2-Ph	Compound 928
R^{11}= 2-OCH_2CO_2H-4-NH_2-Ph	Compound 929
R^{11}= 3-OCH_2CO_2H-2-NH_2-Ph	Compound 930
R^{11}= 2-OCH_2CO_2H-3-NH_2-Ph	Compound 931
R^{11}= 4-$NHCH_2CO_2H$-3-NH_2-Ph	Compound 932
R^{11}= 4-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 933
R^{11}= 3-$NHCH_2CO_2H$-4-NH_2-Ph	Compound 934
R^{11}= 2-$NHCH_2CO_2H$-4-NH_2-Ph	Compound 935
R^{11}= 3-$NHCH_2CO_2H$-2-NH_2-Ph	Compound 936
R^{11}= 2-$NHCH_2CO_2H$-3-NH_2-Ph	Compound 937
R^{11}= 4-$(CH_2)_2CO_2H$-3-OH-Ph	Compound 938
R^{11}= 4-$(CH_2)_2CO_2H$-2-OH-Ph	Compound 939
R^{11}= 2-CO_2H-4-OH-Ph	Compound 940
R^{11}= 2-CO_2H-3-OH-Ph	Compound 941
R^{11}= 4-CO_2H-2-OH-Ph	Compound 942
R^{11}= 4-CO_2H-3-OH-Ph	Compound 943

Compounds wherein R^8=3-NO_2-Ph, R^9=Me, R^{10}=Me, and R^{11} is any one of the substituents shown below.

【Hyo 17】

Table 1-17

R^{11}	Compound No.
R^{11}= 3-NO_2-Ph	Compound 944
R^{11}= 2, 4-$(OH)_2$-Ph	Compound 945
R^{11}= 4-t-Bu-Ph	Compound 946

Compounds wherein R^8=2-Py, R^9=Me, R^{10}=Me, and R^{11} is any one of the substituents shown below.

【Hyo 18】

Table 1-18

R^{11}	Compound No.
R^{11}= 3-NO_2-Ph	Compound 947
R^{11}= 2, 4-$(OH)_2$-Ph	Compound 948

45) Preventive, therapeutic or improving agents for diseases against which activation of the thrombopoietin receptor is effective or platelet increasing agents, which contain thrombopoietin receptor activators represented by Compounds 949 to 1896 which correspond to Compounds 1 to 948 according to 44) in which the methyl group as R^{10} has been replaced by a trifluoromethyl group,

tautomers, prodrugs or pharmaceutically acceptable salts of the activators or solvates thereof, as an active ingredient.

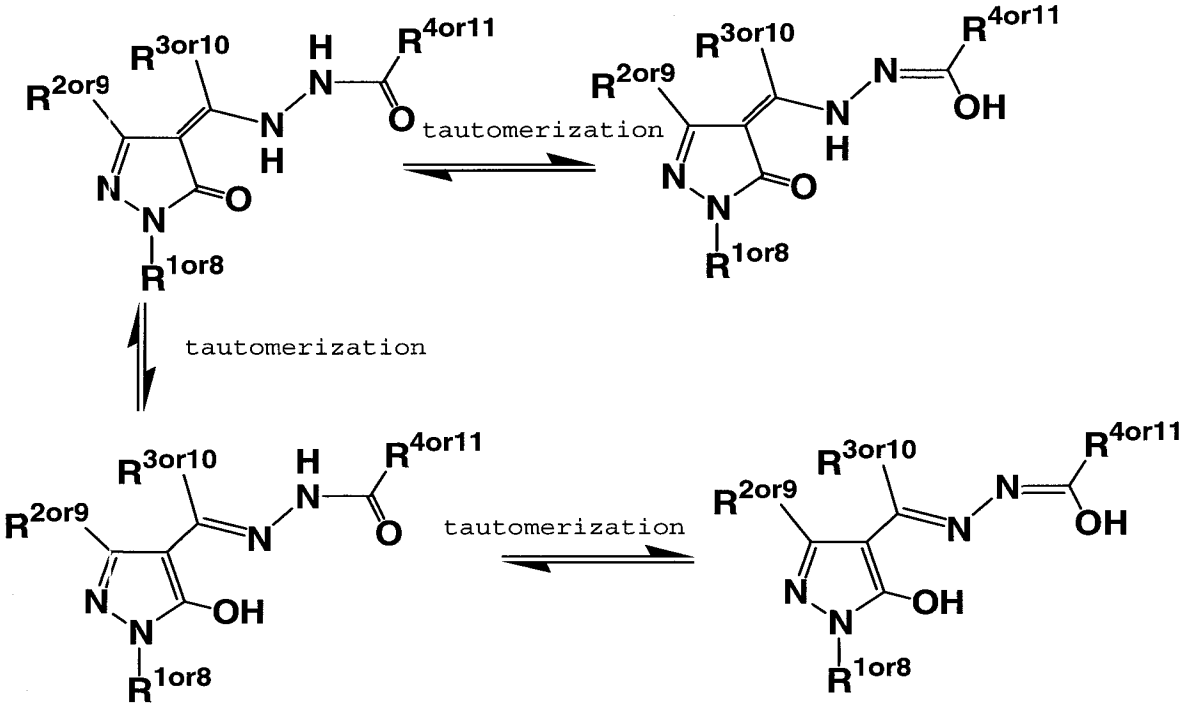
46) Preventive, therapeutic or improving agents for diseases against which activation of the thrombopoietin receptor is effective or platelet increasing agents, which contain thrombopoietin receptor activators represented by Compounds 1897 to 2844 which have the structures corresponding to Compounds 1 to 948 according to 44) in which the methyl group as R^{10} has been replaced by a hydrogen atom, tautomers, prodrugs or pharmaceutically acceptable salts of the activators or solvates thereof, as an active ingredient.

47) Pyrazolone compounds according to 44), which have the structures represented by Compounds 61 to 946, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

48) Pyrazolone compounds according to 45), which have the structures represented by Compounds 1009 to 1894, tautomers, prodrugs or pharmaceutically acceptable salts of the compounds or solvates thereof.

The compounds of the present invention represented by the formula (1) or the formula (2) may be present in the form of pyrazoles which undergo the following tautomerizations, mixtures or mixtures of isomers thereof.

【Ka 6】



The compounds of the present invention represented by the formula (1) or the formula (2) or pharmaceutically acceptable salts thereof may be in the form of arbitrary crystals or arbitrary hydrates. The present invention covers these crystals, hydrates and mixtures. They may be in the form of optional solvates with organic solvents such as acetone, ethanol and tetrahydrofuran, and the present invention covers any of these forms.

The compounds of the present invention represented by the formula (1) or the formula (2) may be converted to pharmaceutically acceptable salts or may be liberated from the resulting salts, if necessary. The pharmaceutically acceptable salts of the present

invention may be, for example, salts with alkali metals (such as lithium, sodium and potassium), alkaline earth metals (such as magnesium and calcium), ammonium, organic bases and amino acids. They may be salts with inorganic acids (such as hydrochloric acid, hydrobromic acid, phosphoric acid and sulfuric acid) and organic acids (such as acetic acid, citric acid, maleic acid, fumaric acid, benzenesulfonic acid and p-toluenesulfonic acid). They may also be complexes with transition metals (such as copper and zinc).

The compounds which serve as prodrugs are derivatives of the present invention having chemically or metabolically degradable groups which give pharmacologically active compounds of the present invention upon solvolysis or under physiological conditions in vivo. Methods for selecting or producing appropriate prodrugs are disclosed, for example, in Design of Prodrug (Elsevier, Amsterdam 1985). In the present invention, when the compound has a hydroxyl group, acyloxy derivatives obtained by reacting the compound with appropriate acyl halides or appropriate acid anhydrides may, for example, be mentioned as a prodrug. Acyloxys particularly preferred as prodrugs include $-OCOC_2H_5$, -OCO(t-Bu), $-OCOC_{15}H_{31}$, $-OCO(m-CO_2Na-Ph)$, $-OCOCH_2CH_2CO_2Na$, $-OCOCH(NH_2)CH_3$, $-OCOCH_2N(CH_3)_2$ and the like. When the compound of the present invention has an amino group, amide derivatives obtained by reacting the

compound having an amino group with appropriate acid halides or appropriate mixed acid anhydrides may, for example, be mentioned as prodrugs. Amides particularly preferred as prodrugs include $-NHCO(CH_2)_{20}OCH_3$, $-NHCOCH(NH_2)CH_3$ and the like. When the compound of the present invention has a carboxyl group, carboxylic acid esters with aliphatic alcohols or carboxylic acid esters obtained by the reaction of an alcoholic free hydroxyl group of 1,2- or 1,3-digylcerides may, for example, be mentioned as prodrugs. Particularly preferred prodrugs are methyl esters and ethyl esters.

The preventive, therapeutic and improving agents for diseases against which activation of the thrombopoietin receptor is effective or platelet increasing agents which contain the thrombopoietin receptor activators, tautomers, prodrugs or pharmaceutically acceptable salts of the activators or solvates thereof as an active ingredient may usually be administered as oral medicines such as tablets, capsules, powder, granules, pills and syrup, as rectal medicines, percutaneous medicines or injections. The agents of the present invention may be administered as a single therapeutic agent or as a mixture with other therapeutic agents. Though they may be administered as they are, they are usually administered in the form of medical compositions. These pharmaceutical preparations can be obtained by adding pharmacologically and pharmaceutically acceptable additives by conventional

methods. Namely, for oral medicines, ordinary excipients, lubricants, binders, disintegrants, humectants, plasticizers and coating agents may be used. Oral liquid preparations may be in the form of aqueous or oily suspensions, solutions, emulsions, syrups or elixirs or may be supplied as dry syrups to be mixed with water or other appropriate solvents before use. Such liquid preparations may contain ordinary additives such as suspending agents, perfumes, diluents and emulsifiers. In the case of rectal administration, they may be administered as suppositories. Suppositories may use an appropriate substance such as cacao butter, laurin tallow, Macrogol, glycerogelatin, Witepsol, sodium stearate and mixtures thereof as the base and may contain an emulsifier, a suspending agent, a preservative and the like. For injections, a solvent or a solubilizing agent such as distilled water for injection, physiological saline, 5% glucose solution and propylene glycol and pharmaceutical components such as a pH regulator, an isotonizing agent and a stabilizer may be used to form aqueous dosage forms or dosage forms which need dissolution before use.

The dose of the agents of the present invention for administration to human is usually about from 0.1 to 1000 mg/human/day in the case of oral drugs or rectal administration and about from 0.05 mg to 500 mg/human/day in the case of injections, though it depends on the age

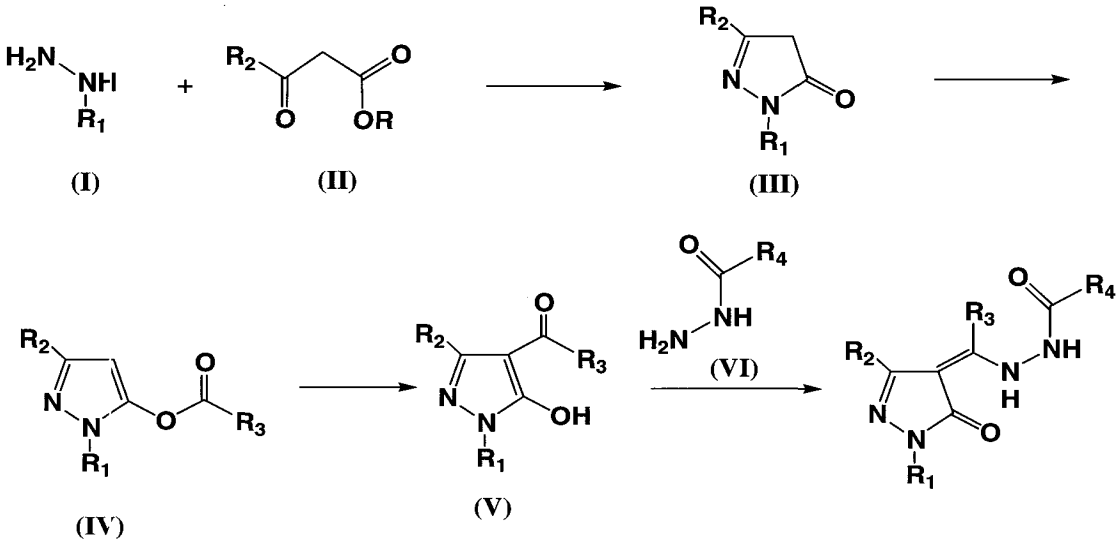
and conditions of the patient. The above-mentioned ranges are mere examples, and the dose should be determined from the conditions of the patient.

The present invention is used when the use of compounds which have thrombopoietin receptor affinity and act as thrombopoietin receptor agonists are expected to improve pathological conditions. For example, hematological disorders accompanied by abnormal platelet count may be mentioned. Specifically, it is effective for therapy or prevention of human and mammalian diseases caused by abnormal megakaryopoiesis, especially those accompanied by thrombocytopenia. Examples of such diseases include thrombocytopenia accompanying chemotherapy or radiotherapy of cancer, thrombocytopenia caused by bone marrow transplantation, surgery and serious infection, or gastrointestinal bleeding, but such diseases are not restricted to these mentioned. Typical thrombocytopenias such as aplastic anemia, idiopathic thrombocytopenic purpura, myelodysplastic syndrome and thrombopoietin deficiency are also targets of the agents of the present invention. The present invention may be used as a peripheral stem cell mobilizer, a megakaryocytic leukemia cell differentiation inducer and a platelet increasing agent for platelet donors. In addition, potential applications include therapeutic angiogenesis based on differentiation and proliferation of vascular endothelial cells and endothelial progenitor

cells, prevention and therapy of arteriosclerosis, myocardial infarction, unstable angina, peripheral artery occlusive disease, but there is no restriction.

The pyrazolone compounds represented by the formula (1) or the formula (2) are prepared by the process illustrated below.

【Ka 7】



The pyrazolones (III) are obtained by known methods (Syn. Comm 20(20), 3213 (1990), Chem Ber 59, 320 (1926), Monatsh. Chem 89, 30 (1958)), for example, by reacting β-keto esters (II) with hydrazines (R^1NHNH_2 or salts thereof) in acetic acid with reflux. Acylation of them with acyl halides (R^3COCl) or acid anhydrides ($(R^3CO)_2O$) to (IV) followed by Fries rearrangement in the presence of potassium carbonate in dioxane with heating gives 4-acyl-5-hydroxypyrazoles (V). They are heated with hydrazides ($R^4CONHNH_2$ (VI) or salts thereof) in a solvent

to give the desired products. The compounds of the present invention are usually obtained with high purity by recrystallization or washing with solvents because they have good crystallizability. However, if necessary, they may be purified by column chromatography, thin layer chromatography, high performance liquid chromatography (HPLC) or high performance liquid chromatography-mass spectrometry (LC-MS).

【Examples】

Now, the present invention will be described in further detail with reference to Examples. However, it should be understood that the present invention is by no means restricted by these specific Examples.

For the compound Nos. in Synthetic Examples, Table 1 should be referred to.

In high performance liquid chromatography-mass spectrometry (LC-MS), the retention time was measured under the following conditions.

Column: Waters XTerra MSC18 4.6×50 mm

Eluent: H_2O:CH_3CN = 85:15 → 15:85

Syntheses of the compounds of Reference Synthetic Examples followed Examples 2-5 (pages 12-14) of WO01/34585.

SYNTHETIC EXAMPLE 1

Synthesis of 2,4-dihydroxybenzoic N'-(1-(3-methyl-5-oxo-1-(4-iodophenyl)-1,5-dihydro-pyrazol-4-ylidene)-ethyl)-hydrazide (Compound 253)

1.03 g (3 mmol) of 1-(5-hydroxy-1-(4-iodophenyl)-3-methyl-1H-pyrazol-4-yl)-ethanone and 505 mg (3 mmol) of 2,4-dihydroxybenzoic hydrazide were dissolved in 50 ml of DMSO and heated at 85°C for 9 hours with stirring. After cooling and evaporation of the solvent, the crude product was recrystallized from chloroform/ether to give 1.39 g of the desired product as a pale brown solid (yield 94%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.36 (s, 3H), 2.42 (s, 3H), 2.54(s, 3H), 6.36 (t, 1H, J = 2 Hz), 6.40 (d, 1H, J = 2 Hz), 7.68-7.76 (m, 3H), 7.86 (d, 2H, J = 9 Hz)

LC/MS

M^+ = 492.27 (2.88 min)

SYNTHETIC EXAMPLE 2

Synthesis of 3,5-dihydroxybenzoic N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide (Compound 66)

From 1-(1-(4-tert-butylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)-ethanone and 3,5-dihydroxybenzoic hydrazide, 40.1 mg of the desired product was obtained in the same manner as in Synthetic Example 1 as a yellow solid (yield 40%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 1.29 (s, 9H), 2.36 (s, 3H), 2.41 (s, 3H), 6.45 (s, 1H), 6.76 (s, 2H), 7.41 (d, 2H, J = 8.8 Hz), 7.89 (d, 2H, J = 8.8 Hz), 9.65 (s, 2H), 11.08 (s, 1H).

LC/MS

M^+ = 422 (2.19 min).

SYNTHETIC EXAMPLE 3

Synthesis of 3,5-dihydroxybenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide (Compound 129)

From 1-(1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)-ethanone and 3,5-dihydroxybenzoic hydrazide, 57.0 mg of the desired product was obtained in the same manner as in Synthetic Example 1 as a pale red solid (yield 73%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.21 (s, 3H), 2.24 (s, 3H), 2.35 (s, 3H), 2.41 (s, 3H), 6.45 (s, 1H), 6.75 (s, 1H), 6.76(s,1H), 7.14 (d, 1H, J = 8.3 Hz), 7.70 (dd, 1H, J = 1.9, 8.3 Hz), 7.77 (d, 1H, J = 1.9 Hz), 9.66 (s, 2H), 11.09 (s, 1H).

LC/MS

M^+ = 394 (1.82 min).

SYNTHETIC EXAMPLE 4

Synthesis of 4-methoxycarbonyl-benzoic N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide (Compound 118)

1) Synthesis of 4-methoxycarbonylbenzhydrazide

The known procedure disclosed in the literature (Synthetic Communications, 28(7), 1223-1231, (1998)) was followed using monomethyl terephthalate and tetramethylfluoroformamidinium hexafluorophosphate to give 1.36 g of a colorless solid (yield 70%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 3.86 (s, 3H), 4.56 (s, 2H), 7.93 (d, 2H, J = 8.3 Hz), 8.02 (d, 2H, J = 8.3 Hz), 9.96 (bs, 1H).

2) Synthesis of 4-methoxycarbonylbenzoic N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

30.5 mg (0.11 mmol) of 1-(1-(4-tert-butylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)-ethanone and 23.1 mg (0.11 mmol) of 4-methoxycarbonylbenzhydrazide were dissolved in 3.0 ml of DMF and stirred at 100°C for 3 hours. After cooling and evaporation of the solvent, the crude product was recrystallized from ethyl acetate/n-hexane to give 32.9 mg of the desired product as a yellow solid (yield 66%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 1.29 (s, 9H), 2.37 (s, 3H), 2.46 (s, 3H), 3.90 (s, 3H), 7.41 (d, 2H, J = 8.7 Hz), 7.89 (d, 2H, J = 8.7 Hz), 8.05 (d, 2H, J = 8.4 Hz), 8.12 (d, 2H, J = 8.4 Hz).

LC/MS

M^+ = 448 (2.64 min).

SYNTHETIC EXAMPLE 5

Synthesis of 4-carboxybenzoic N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide (Compound 75)

To 23.2 mg (0.05 mmol) of the 4-methoxycarbonylbenzoic N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-

hydrazide synthesized in Synthetic Example 4 in 2.0 ml of methanol, 255 µl (0.255 mmol) of 1 mol/L aqueous sodium hydroxide was added at room temperature, and the mixture was heated at from 60°C to 80°C for 3.5 hours. After it was cooled to room temperature, 255 µl (0.255 mmol) of 1M hydrochloric acid was added, and the precipitated solid was collected by filtration to obtain 13.9 mg of the desired product as a pale brown solid (yield 61%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 1.29 (s, 9H), 2.37 (s, 3H), 2.45 (s, 3H), 7.41 (d, 2H, J = 8.7 Hz), 7.89 (d, 2H, J = 8.7 Hz), 8.03 (d, 2H, J = 8.3 Hz), 8.09 (d, 2H, J = 8.3 Hz), 11.44 (s, 1H).

LC/MS

M^+ = 434 (2.38 min).

SYNTHETIC EXAMPLE 6

Synthesis of 4-methoxycarbonylbenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide (Compound 181)

From 1-(1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)-ethanone and 4-methoxycarbonylbenzhydrazide, 53.0 mg of the desired product was obtained in the same manner as in Synthetic Example 4 as a pale yellow solid (yield 64%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.21 (s, 3H), 2.25 (s, 3H), 2.36 (s, 3H), 2.45 (s, 3H), 3.89 (s, 3H), 7.14 (d, 1H, J = 8.5 Hz), 7.71 (dd, 1H, J = 1.9, 8.5 Hz), 7.77 (d, 1H, J = 1.9 Hz), 8.05 (d, 2H,

J = 8.5 Hz), 8.12 (d, 2H, J = 8.5 Hz).

LC/MS

M^+ = 420 (2.34 min).

SYNTHETIC EXAMPLE 7

Synthesis of 4-carboxybenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide (Compound 138)

From the 4-methoxycarbonylbenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide synthesized in Synthetic Example 6, 21.5 mg of the desired product was obtained in the same manner as in Synthetic Example 5 as a pale yellow solid (yield 71%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.21 (s, 3H), 2.25 (s, 3H), 2.36 (s, 3H), 2.45 (s, 3H), 7.14 (d, 1H, J = 8.3 Hz), 7.70 (dd, 1H, J = 1.9, 8.3 Hz), 7.77 (d, 1H, J = 1.9 Hz), 8.03 (d, 2H, J = 8.3 Hz), 8.10 (d, 2H, J = 8.3 Hz), 11.45 (s, 1H).

LC/MS

M^+ = 406 (2.03 min).

SYNTHETIC EXAMPLE 8

Synthesis of 4-methoxycarbonylbenzoic N'-(1-(3-methyl-5-oxo-1-(3-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide (Compound 366)

From 1-(5-hydroxy-3-methyl-1-(3-trifluoromethylphenyl)-1H-pyrazol-4-yl)-ethanone and 4-methoxycarbonylbenzhydrazide, 59.9 mg of the desired

product was obtained in the same manner as in Synthetic Example 4 as a yellow solid (yield 65%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.40 (s, 3H), 2.51 (s, 3H), 3.91 (s, 3H), 7.49 (d, 1H, J = 7.4 Hz), 7.66 (dd, 1H, J = 8.0, 8.3 Hz), 8.06 (d, 2H, J = 8.3 Hz), 8.13 (d, 2H, J = 8.3 Hz), 8.29 (d, 1H, J = 8.0 Hz), 8.45 (s, 1H), 11.55 (bs, 1H), 12.47 (bs, 1H).

LC/MS

M^+ = 460.41 (2.69 min).

SYNTHETIC EXAMPLE 9

Synthesis of 4-carboxybenzoic N'-(1-(3-methyl-5-oxo-1-(3-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide (Compound 323)

From the 4-methoxycarbonylbenzoic N'-(1-(3-methyl-5-oxo-1-(3-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide synthesized in Synthetic Example 8, 26.5 mg of the desired product was obtained in the same manner as in Synthetic Example 5 as a pale yellow solid (yield 78%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.41 (s, 3H), 2.51 (s, 3H), 7.49 (d, 1H, J = 8.0 Hz), 7.66 (dd, 1H, J = 8.0 Hz), 8.03 (d, 2H, J = 8.3 Hz), 8.10 (d, 2H, J = 8.3 Hz), 8.29 (d, 1H, J = 8.0 Hz), 8.45 (s, 1H), 11.52 (bs, 1H), 12.46 (bs, 1H).

LC/MS

M^+ = 446.38 (2.29 min).

SYNTHETIC EXAMPLE 10

Synthesis of 4-methoxycarbonylbenzoic N'-(1-(3-methyl-5-oxo-1-(4-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide (Compound 427)

From 1-(5-hydroxy-3-methyl-1-(4-trifluoromethylphenyl)-1H-pyrazol-4-yl)-ethanone and 4-methoxycarbonylbenzhydrazide, 58.9 mg of the desired product was obtained in the same manner as in Synthetic Example 4 as a yellow solid (yield 65%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.40 (s, 3H), 2.51 (s, 3H), 3.91 (s, 3H), 7.77 (d, 2H, J = 8.5 Hz), 8.06 (d, 2H, J = 8.5 Hz), 8.13 (d, 2H, J = 8.5 Hz), 8.26 (d, 2H, J = 8.5 Hz), 11.56 (bs, 1H), 12.46 (bs, 1H).

LC/MS

M^+ = 460.41 (2.62 min).

SYNTHETIC EXAMPLE 11

Synthesis of 4-carboxybenzoic N'-(1-(3-methyl-5-oxo-1-(4-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide (Compound 384)

From the 4-methoxycarbonylbenzoic N'-(1-(3-methyl-5-oxo-1-(4-trifluoromethylphenyl)-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide synthesized in Synthetic Example 10, 18.6 mg of the desired product was obtained in the same manner as in Synthetic Example 5 as a pale yellow solid (yield 68%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.40 (s, 3H), 2.51 (s, 3H), 7.77 (d, 2H, J = 8.7 Hz), 8.03 (d, 2H, J = 8.2 Hz), 8.10 (d, 2H, J = 8.2 Hz), 8.23 (d, 2H, J = 8.7 Hz), 11.53 (bs, 1H), 12.45 (bs, 1H).

LC/MS

M^+ = 446.38 (2.31 min).

SYNTHETIC EXAMPLE 12

Synthesis of 3-carboxybenzoic N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide (Compound 74)

1) Synthesis of 3-methoxycarbonylbenzhydrazide

The procedure in Synthetic Example 4 was followed using monomethyl isophthalate and tetramethylfluoroformamidinium hexafluorophosphate to give 244.6 mg of a yellow solid (yield > 99%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 3.89 (s, 3H), 4.61 (bs, 2H), 7.62 (dd, 1H, J = 8.0 Hz), 8.08 (dd, 2H, J = 1.8, 8.0 Hz), 8.42 (d, 1H, J = 1.8 Hz), 9.98 (bs, 1H).

LC/MS

M^+ = 194 (0.51 min).

2) Synthesis of 3-methoxycarbonylbenzoic N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

From 1-(1-(4-tert-butylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)-ethanone and 3-methoxycarbonylbenzhydrazide, 64.6 mg of the desired product was obtained in the same manner as in Synthetic Example 4 as a yellow solid (yield

70%).

3) Synthesis of 3-carboxybenzoic N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

From the 3-methoxycarbonylbenzoic N'-(1-(1-(4-tert-butylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide synthesized in 2), 11.2 mg of the desired product was obtained in the same manner as in Synthetic Example 5 as a pale brown solid (yield 50%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 1.29 (s, 9H), 2.37 (s, 3H), 2.45 (s, 3H), 7.42 (d, 2H, J = 8.8 Hz), 7.70 (dd, 1H, J = 7.8 Hz), 7.89 (d, 2H, J = 8.8 Hz), 8.16 (d, 1H, J = 6.9 Hz), 8.51 (s, 1H), 11.46 (bs, 1H).

LC/MS

M^+ = 434.49 (2.37 min).

SYNTHETIC EXAMPLE 13

Synthesis of 3-carboxybenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide (Compound 137)

1) Synthesis of 3-methoxycarbonylbenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

From 1-(1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)-ethanone and 3-methoxycarbonylbenzhydrazide, 27.4 mg of the desired product was obtained in the same manner as in Synthetic Example 4 as a pale yellow solid

(yield 35%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.21 (s, 3H), 2.25 (s, 3H), 2.34 (s, 3H), 2.36 (s, 3H), 3.92 (s, 3H), 7.14 (d, 1H, J = 8.3 Hz), 7.70—7.77 (m, 3H), 8.20 (d, 2H, J = 8.0 Hz), 8.51 (s, 1H), 11.49 (s, 1H).

2) Synthesis of 3-carboxybenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide

From the 3-methoxycarbonylbenzoic N'-(1-(1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)-ethyl)-hydrazide synthesized in 1), 17.2 mg of the desired product was obtained in the same manner as in Synthetic Example 5 as a pale yellow solid (yield 68%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.21 (s, 3H), 2.25 (s, 3H), 2.36 (s, 3H), 2.45 (s, 3H), 7.14 (d, 1H, J = 8.5 Hz), 7.68—7.77 (m, 3H), 8.15-8.20 (m, 2H), 8.19 (d, 1H, J = 7.2 Hz), 8.50 (s, 1H).

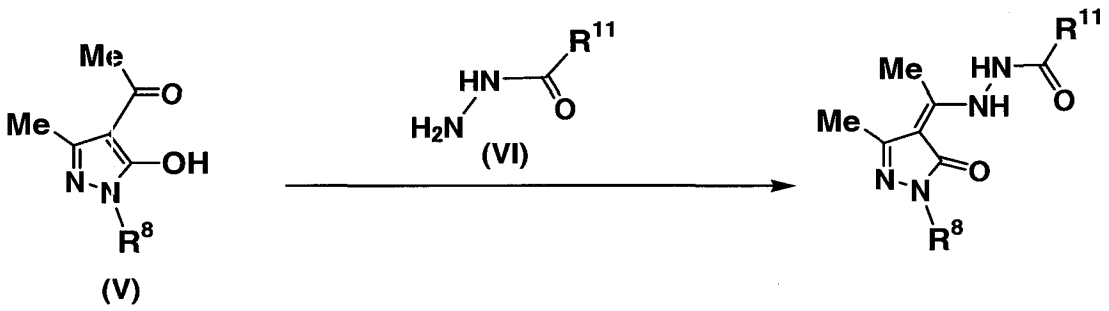
LC/MS

M^+ = 406.43 (2.03 min).

SYNTHETIC EXAMPLES 14 to 92

The structural formulae, yields, appearances, and molecular weights measured by LC/MS of the compounds synthesized by the following method based on Synthetic Example 1 are shown in Table 2.

【Ka 8】



A pyrazole derivative (V) and a benzoic hydrazide (VI) were dissolved in a solvent such as DMF, EtOH and DMSO in a molar ratio of 1:1 and heated at 80 to 100°C with stirring. The solvent was removed by evaporation, and the resulting crude product was dissolved in chloroform and recrystallized from a poor solvent or washed with chloroform to give the desired product.

【Hyo 19】

Table 2

Synthetic Ex. No.	Comp. No.	R^8	R^{11}	Yield	Appearance	Molecular weight
14	9	Ph	3-NO_2-Ph	37.6%	Yellow solid	379.38
15	69	4-t-Bu-Ph	3-NO_2-Ph	58.1%	Pale brown solid	435.48
16	1	Ph	2-OH-Ph	24.7%	Pale yellow solid	350.38
17	3	Ph	4-OH-Ph	65.1%	Pale pink solid	350.38
18	58	Ph	3-OH-2-Naphthyl	59.2%	Pale yellow solid	400.44
19	5	Ph	2,4-$(OH)_2$-Ph	41.1%	Pale yellow solid	366.38
20	4	Ph	3,4-$(OH)_2$-Ph	43.9%	Pale brown solid	366.38
21	59	Ph	2-NO_2-Ph	67.5%	Yellow solid	379.38
22	60	Ph	4-NO_2-Ph	53.4%	Yellow solid	379.38
23	61	4-t-Bu-Ph	2-OH-Ph	29.4%	Pale yellow solid	406.48
24	63	4-t-Bu-Ph	4-OH-Ph	24.1%	Pale brown solid	406.48
25	119	4-t-Bu-Ph	3-OH-2-Naphthyl	11.0%	Yellow solid	456.54

	26	65	4-t-Bu-Ph	2,4-$(OH)_2$-Ph	27.5%	Pale yellow solid	422.48
	27	64	4-t-Bu-Ph	3,4-$(OH)_2$-Ph	40.2%	Brown solid	422.48
5	28	120	4-t-Bu-Ph	2-NO_2-Ph	51.4%	Pale yellow solid	435.48
	29	121	4-t-Bu-Ph	4-NO_2-Ph	49.9%	Yellow solid	435.48
10	30	370	4-CF_3-Ph	2-OH-Ph	48.5%	Yellow solid	418.37
	31	372	4-CF_3-Ph	4-OH-Ph	60.0%	Pink solid	418.37
	32	428	4-CF_3-Ph	3-OH-2-Naphthyl	8.2%	Pale yellow solid	468.43
15	33	374	4-CF_3-Ph	2,4-$(OH)_2$-Ph	3.1%	Brown solid	434.37
	34	373	4-CF_3-Ph	3,4-$(OH)_2$-Ph	73.2%	Pale pink solid	434.37
20	35	429	4-CF_3-Ph	2-NO_2-Ph	68.8%	Pale pink solid	447.37
	36	378	4-CF_3-Ph	3-NO_2-Ph	64.2%	Pale yellow solid	447.37
	37	430	4-CF_3-Ph	4-NO_2-Ph	60.1%	Pale yellow solid	447.37
25	38	249	4-I-Ph	2-OH-Ph	22.9%	Yellow solid	476.27
	39	251	4-I-Ph	4-OH-Ph	36.6%	Pale brown solid	476.27
30	40	306	4-I-Ph	3-OH-2-Naphthyl	46.5%	Yellow solid	526.33

	41	252	4-I-Ph	3,4-$(OH)_2$-Ph	52.5%	Pale pink solid	492.27
	42	307	4-I-Ph	2-NO_2-Ph	43.3%	Pale pink solid	505.27
5	43	257	4-I-Ph	3-NO_2-Ph	51.4%	Yellow solid	505.27
	44	308	4-I-Ph	4-NO_2-Ph	27.6%	Yellow solid	505.27
	45	309	3-CF_3-Ph	2-OH-Ph	69.4%	Pale yellow solid	418.37
10							
	46	311	3-CF_3-Ph	4-OH-Ph	25.7%	Pale brown solid	418.37
	47	367	3-CF_3-Ph	3-OH-2-Naphthyl	54.3%	Pale yellow solid	468.43
15	48	313	3-CF_3-Ph	2,4-$(OH)_2$-Ph	13.2%	Pale brown solid	434.37
	49	312	3-CF_3-Ph	3,4-$(OH)_2$-Ph	57.3%	Pale pink solid	434.37
	50	368	3-CF_3-Ph	2-NO_2-Ph	53.9%	Pink solid	447.37
20							
	51	317	3-CF_3-Ph	3-NO_2-Ph	57.4%	Pale yellow solid	447.37
	52	369	3-CF_3-Ph	4-NO_2-Ph	32.2%	Pale yellow solid	447.37
25	53	124	3,4-Me_2-Ph	2-OH-Ph	52.2%	Pale yellow solid	378.43
	54	126	3,4-Me_2-Ph	4-OH-Ph	66.2%	Pale pink solid	378.43
	55	182	3,4-Me_2-Ph	3-OH-2-Naphthyl	65.9%	Pale yellow solid	428.49
30							

	56	128	3,4-Me_2-Ph	2,4-$(OH)_2$-Ph	43.0%	Pale yellow solid	394.43
	57	127	3,4-Me_2-Ph	3,4-$(OH)_2$-Ph	40.4%	Pale yellow solid	394.43
	58	183	3,4-Me_2-Ph	2-NO_2-Ph	67.9%	Pale yellow solid	407.43
	59	132	3,4-Me_2-Ph	3-NO_2-Ph	50.8%	Pale yellow solid	407.43
	60	184	3,4-Me_2-Ph	4-NO_2-Ph	67.1%	Pale brown solid	407.43
	61	187	3,4-Cl_2-Ph	2-OH-Ph	45.6%	Pale yellow solid	419.27
	62	189	3,4-Cl_2-Ph	4-OH-Ph	63.7%	Pale yellow solid	419.27
	63	244	3,4-Cl_2-Ph	3-OH-2-Naphthyl	51.1%	Pale brown solid	469.33
	64	191	3,4-Cl_2-Ph	2,4-$(OH)_2$-Ph	17.0%	Pale yellow solid	435.27
	65	190	3,4-Cl_2-Ph	3,4-$(OH)_2$-Ph	66.1%	Pale pink solid	435.27
	66	245	3,4-Cl_2-Ph	2-NO_2-Ph	67.4%	Pale yellow solid	448.27
	67	195	3,4-Cl_2-Ph	3-NO_2-Ph	64.5%	Pale yellow solid	448.27
	68	246	3,4-Cl_2-Ph	4-NO_2-Ph	51.1%	Brown solid	448.27
	69	72	4-t-Bu-Ph	4-NH_2-Ph	74.8%	Pale brown solid	405.53
	70	71	4-t-Bu-Ph	3-NH_2-Ph	48.7%	Pale brown solid	405.53

71	122	4-t-Bu-Ph	4-CF_3-Ph	69.1%	Pale yellow solid	458.49
72	123	4-t-Bu-Ph	4-t-Bu-Ph	77.9%	Pink solid	446.63
73	135	3,4-Me_2-Ph	4-NH_2-Ph	92.7%	Red solid	377.48
74	134	3,4-Me_2-Ph	3-NH_2-Ph	61.1%	Pale orange solid	377.48
75	185	3,4-Me_2-Ph	4-CF_3-Ph	67.7%	Pale orange solid	430.44
76	186	3,4-Me_2-Ph	4-t-Bu-Ph	66.8%	Pale pink solid	418.58
77	198	3,4-Cl_2-Ph	4-NH_2-Ph	51.2%	Orange solid	418.32
78	197	3,4-Cl_2-Ph	3-NH_2-Ph	69.7%	Pink solid	418.32
79	247	3,4-Cl_2-Ph	4-CF_3-Ph	69.6%	Pale orange solid	471.28
80	248	3,4-Cl_2-Ph	4-t-Bu-Ph	79.8%	Pale pink solid	459.42
81	62	4-t-Bu-Ph	3-OH-Ph	72.3%	Pale yellow solid	406.53
82	125	3,4-Me_2-Ph	3-OH-Ph	42.0%	Pale pink solid	378.48
83	188	3,4-Cl_2-Ph	3-OH-Ph	89.0%	Pink solid	419.32
84	944	3-NO_2-Ph	3-NO_2-Ph	58%	Brown solid	424.57
85	947	2-Py	3-NO_2-Ph	63%	Pale orange solid	380.36

86	945	3-NO_2-Ph	2,4-$(OH)_2$-Ph	43%	Brown solid	411.37
87	948	2-Py	2,4-$(OH)_2$-Ph	66%	Pale yellow solid	367.36
88	946	3-NO_2-Ph	4-t-Bu-Ph	25%	Brown solid	435.48
89	319	3-CF_3-Ph	3-NH_2-Ph	74%	Pale brown solid	417.38
90	320	3-CF_3-Ph	4-NH_2-Ph	82%	Pale orange solid	417.38
91	380	4-CF_3-Ph	3-NH_2-Ph	69%	Brown solid	417.38
92	381	4-CF_3-Ph	4-NH_2-Ph	72%	Pale pink solid	417.38

SYNTHETIC EXAMPLE 93

Synthesis of 2,4-dihydroxybenzoic N'-(1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene-methyl)-hydrazide (Compound 2024)

1) Synthesis of 1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazole-4-carbaldehyde

1.86 g (9.16 mmol) of 1-(3,4-dimethylphenyl)-3-methyl-3-pyrazolin-5-one was dissolved in 3.6 ml of dry dimethylformamide, and 1.02 ml (11.0 mmol) of phosphorus oxychloride was added gradually under cooling with ice at 20°C or below. After the addition, the mixture was heated at 100°C for 2 hours, cooled to room temperature and poured into 30 ml of ice-cold water. Then, the mixture was washed with 10 ml of water and 10 ml of

dimethylformamide. The mixed solution was stirred for 18 hours, and the precipitated solid was collected by filtration, washed with 20 ml of water and dried to obtain 1.03 g of the desired product as a pale brown solid (yield 49%).

^{1}H-NMR (ppm in $CDCl_3$)

δ = 2.29 (s, 3H), 2.32 (s, 3H), 2.43 (s, 3H), 7.20 (d, 1H, J = 8 Hz), 7.48 (dd, 1H, J = 8 Hz, 2 Hz), 7.54 (d, 1H, J = 2 Hz), 9.60 (s, 1H)

2) Synthesis of 2,4-dihydroxybenzoic N'-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene-methyl]-hydrazide

46 mg (0.2 mmol) of the 1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazole-4-carbaldehyde synthesized in 1) and 34 mg (0.20 mmol) of 2,4-dihydroxybenzoic hydrazide were stirred in 1 ml of ethanol at room temperature for 96 hours. The precipitated solid was collected by filtration and washed with 1 ml of ethanol, 1 ml of ether and 1 ml of methanol successively to obtain 53 mg of the desired product (yield 70%).

LC/MS

M^+ = 380.40 (2.77 min)

REFERENCE SYNTHETIC EXAMPLE 1 (EXAMPLE 4 OF WO01/34585)

Synthesis of 5-(4-carboxybenzylidene)-3-[(1-{3,4-dimethylphenyl}-5-hydroxy-3-methyl-1H-pyrazol-4-ylmethylene)amino]-2-thioxothiazolidin-4-one

1) Synthesis of 1-(3,4-dimethylphenyl)-5-hydroxy-3-

methyl-1H-pyrazole-4-carbaldehyde

1.86 g (9.16 mmol) of 1-(3,4-dimethylphenyl)-3-methyl-3-pyrazolin-5-one was dissolved in 3.6 ml of dry dimethylformamide, and 1.02 ml (11.0 mmol) of phosphorus oxychloride was added gradually under cooling with ice at 20°C or below. After the addition, the mixture was heated at 100°C for 2 hours, then cooled to room temperature and poured into 30 ml of ice-cold water. Then, it was washed with 10 ml of water and 10 ml of dimethylformamide. The mixed solution was stirred for 18 hours, and the precipitated solid was collected by filtration, washed with 20 ml of water and dried to obtain 1.03 g of the above-identified desired product as a pale brown solid (yield 49%).

^{1}H-NMR (ppm in $CDCl_3$)

δ = 2.29 (s, 3H), 2.32 (s, 3H), 2.43 (s, 3H), 7.20 (d, 1H, J = 8 Hz), 7.48 (dd, 1H, J = 8 Hz, 2Hz), 7.54 (d, 1H, J = 2 Hz), 9.60 (s, 1H)

2) Synthesis of 5-(4-carboxybenzylidene)-3-[(1-{3,4-dimethylphenyl}-5-hydroxy-3-methyl-1H-pyrazol-4-ylmethylene)amino]-2-thioxothiazolidin-4-one

230 mg (1 mmol) of the 1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazole-4-carbaldehyde synthesized in 1) and 148 mg (1 mmol) of 3-aminorhodanine were stirred in 10 ml of ethanol at room temperature for 96 hours. The resulting solid was collected by filtration, washed with ethanol and ether and dried to obtain 332 mg

of a crude imine.

A liquid mixture of 160 mg (0.444 mmol) of the imine, 4 mg of piperidine, 66 mg of 4-formylbenzoic acid, 6 mg of benzoic acid and 20 ml of toluene was refluxed in a reactor equipped with a Dean-Stark tube packed with molecular sieve for 7 hours with heating. After cooling, the precipitated solid was collected by filtration and washed with 3 ml of toluene and 3 ml of ether to obtain 23.3 mg of a yellow solid. It was washed with a liquid mixture of methanol and chloroform to obtain 16.5 mg of the desired product (yield 7.5%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.10-2.40 (s×3, 9H), 7.18(d, 1H, J = 8 Hz), 7.63 (d, 1H, J = 8 Hz), 7.67 (s, 1H), 7.84 (d, 2H, J = 8 Hz), 8.03 (d, 2H, J = 8 Hz), 8.10 (d, 2H, J = 8 Hz), 8.20 (s, 1H)

LC/MS

M^+ = 493.0 (3.33 min)

REFERENCE SYNTHETIC EXAMPLE 2 (EXAMPLE 5 OF WO01/34585)

Synthesis of 5-(3-carboxybenzylidene)-3-[(1-{3,4-dimethylphenyl}-5-hydroxy-3-methyl-1H-pyrazol-4-ylmethylene)amino]-2-thioxothiazolidin-4-one

A liquid mixture of 160 mg (0.444 mmol) of the imine synthesized in 2) of Reference Synthetic Example 1, 4 mg of piperidine, 66 mg of 3-formylbenzoic acid, 6 mg of benzoic acid and 20 ml of toluene was refluxed in a reactor equipped with a Dean-Stark tube packed with molecular sieve for 7 hours with heating. After cooling,

the precipitated solid was collected by filtration and washed with 3 ml of toluene and 3 ml of ether to obtain 38.5 mg of a yellow solid (yield 18%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.00-2.30 (s×3, 9H), 7.18 (d, 1H, J = 8 Hz), 7.64 (d, 1H, J = 8 Hz), 7.68 (s, 1H), 7.73 (t, 1H, J = 8 Hz), 7.97 (d, 2H, J = 8 Hz), 8.06 (s, 1H), 8.08 (d, 1H, J = 8 Hz), 8.23 (d, 2H, J = 8 Hz)

LC/MS

M^+ = 493.0 (3.32 min)

REFERENCE SYNTHETIC EXAMPLE 3 (EXAMPLE 2 OF WO01/34585)

Synthesis of 3-(3-carboxyphenyl)-1-[(1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-ylmethylene)amino]-2-thioxoimidazolidin-4-one

1) Synthesis of 1-amino-3-(3-carboxyphenyl)-2-thioxoimidazolidin-4-one

179 mg (1 mmol) of 3-isothiocyanatobenzoic acid and 523 µl (3 mmol) of diisopropylethylamine were stirred in 8 ml of dichloromethane and then with 155 mg (1 mmol) of ethyl hydrazinoacetate hydrochloride at room temperature for 96 hours. After the solvent was concentrated, the mixture was partitioned between ethyl acetate and 30% acetic acid. The aqueous layer was extracted with ethyl acetate again, and the organic layers were combined, washed with water and then with saturated aqueous sodium chloride, dried over magnesium sulfate and concentrated. The resulting solid was mixed with a 190:10:0.8 liquid

mixture of ethyl acetate, methanol and acetic acid, and the insoluble was dried to obtain 55.7 mg of the desired product (yield 22%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 4.44 (s, 2H), 5.46 (s, 2H), 7.57 (dd, 1H, J = 8 Hz, J = 1.5 Hz), 7.63 (t, 1H, J = 8 Hz), 7.90 (s, 1H), 7.99(d, 1H, J = 8 Hz)

LC/MS

M^+ = 251.30 (0.59 min).

2) Synthesis of 3-(3-caboxyphenyl)-1-[(1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-ylmethylene)amino]-2-thioxoimidazolidin-4-one

50 mg (0.2 mmol) of the 1-amino-3-(3-carboxyphenyl)-2-thioxoimidazolidin-4-one synthesized above in 1) and 55 mg (0.22 mmol) of the 1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazole-4-carbaldehyde synthesized in 1) of Reference Synthetic Example 1 were stirred in a liquid mixture of 10 ml of ethanol and 5 ml of methanol at room temperature for 96 hours. The resulting insoluble was collected by filtration to obtain 73 mg of the desired product as a yellow solid (yield 72%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.24 (s, 3H), 2.27 (s, 3H), 2.38 (s, 3H), 4.74 (s, 2H), 7.21 (d, 1H, J = 8 Hz), 7.40-7.80 (m, 4H), 7.95 (s, 1H), 8.02 (d, 1H, J = 8 Hz), 8.14 (s, 1H)

LC/MS

M^+ = 463.51 (2.77 min).

REFERENCE SYNTHETIC EXAMPLE 4 (EXAMPLE 3 OF WO01/34585)

Synthesis of 3-(4-carboxyphenyl)-1-[(1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-ylmethylene)amino]-2-thioxoimidazolidin-4-one

1) Synthesis of 1-amino-3-(4-carboxyphenyl)-2-thioxoimidazolidin-4-one

179 mg (1 mmol) of 4-isothiocyanatobenzoic acid and 523 µl (3 mmol) of diisopropylethylamine were stirred in 8 ml of dichloromethane and then with 155 mg (1 mmol) of ethyl hydrazinoacetate hydrochloride at room temperature for 96 hours. After the solvent was concentrated, the mixture was partitioned between ethyl acetate and 30% acetic acid. The aqueous layer was extracted with ethyl acetate again, and the organic layers were combined, washed with water and then with saturated aqueous sodium chloride, dried over magnesium sulfate and concentrated. The resulting solid was mixed with a 190:10:0.8 liquid mixture of ethyl acetate, methanol and acetic acid, and the insoluble was dried to obtain 132 mg of the desired product (yield 53%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 4.46(s, 2H), 5.47 (s, 2H), 7.46 (d, 2H, J = 8 Hz), 8.04 (d, 2H, J = 8 Hz)

LC/MS

M^+ = 251.26 (0.95 min).

2) Synthesis of 3-(4-carboxyphenyl)-1-[(1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-

ylmethylene)amino]-2-thioxoimidazolidin-4-one

50 mg (0.2 mmol) of the 1-amino-3-(4-carboxyphenyl)-2-thioxoimidazolidin-4-one synthesized above in 1) and 55 mg (0.22 mmol) of the 1-(3,4-dimethylphenyl)-5-hydroxy-3-methyl-1H-pyrazole-4-carbaldehyde synthesized in 1) of Reference Synthetic Example 1 were stirred in a liquid mixture of 10 ml of ethanol and 5 ml of methanol at room temperature for 96 hours. The resulting insoluble was collected by filtration to obtain 87 mg of the desired product as a yellow solid (yield 85%).

^{1}H-NMR (ppm in DMSO-d_6)

δ = 2.24 (s, 3H), 2.27 (s, 3H), 2.50 (s, 3H), 4.75 (s, 2H), 7.21 (d, 1H, J = 8 Hz), 7.40-7.70 (m, 4H), 8.08 (d, 2H, J = 8.8 Hz), 8.14 (brs, 1H)

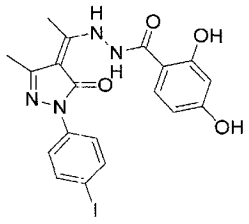
LC/MS

M^+ = 463.51 (2.76 min).

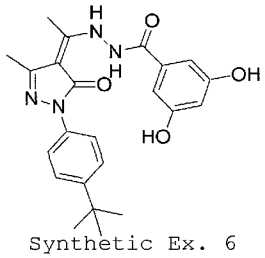
The structural formulae of the compounds obtained in the Synthetic Examples are as follows.

【Ka 9】

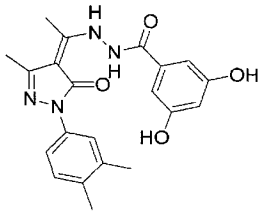
Synthetic Ex. 1 (Compound 253)



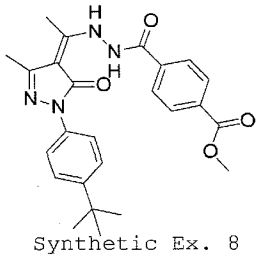
Synthetic Ex. 2 (Compound 66)



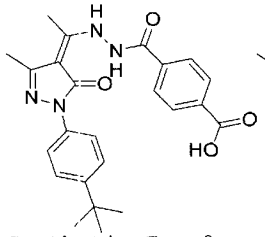
Synthetic Ex. 3 (Compound 129)



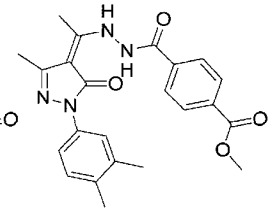
Synthetic Ex. 4 (Compound 118)



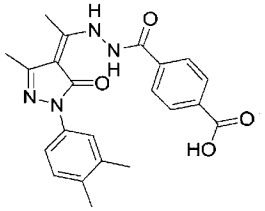
Synthetic Ex. 5 (Compound 75)



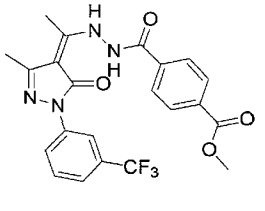
Synthetic Ex. 6 (Compound 181)



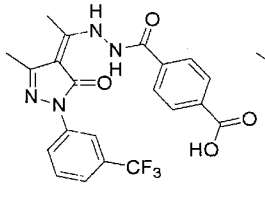
Synthetic Ex. 7 (Compound 138)



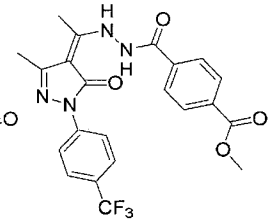
Synthetic Ex. 8 (Compound 366)



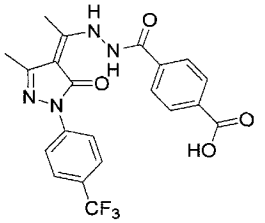
Synthetic Ex. 9 (Compound 323)



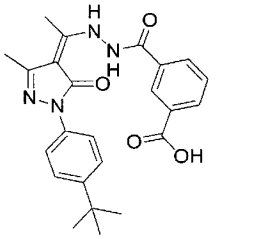
Synthetic Ex. 10 (Compound 427)



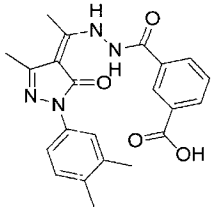
Synthetic Ex. 11 (Compound 384)



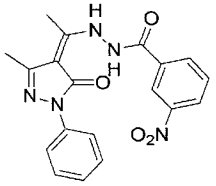
Synthetic Ex. 12 (Compound 74)



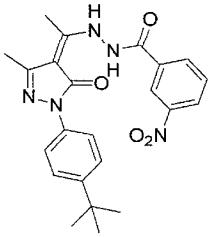
Synthetic Ex. 13 (Compound 137)



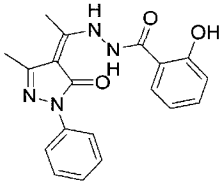
Synthetic Ex. 14 (Compound 9)



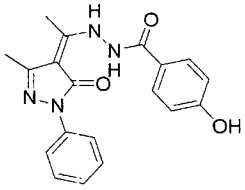
Synthetic Ex. 15 (Compound 69)



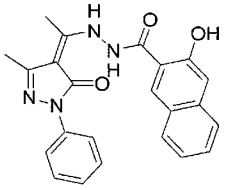
Synthetic Ex. 16 (Compound 1)



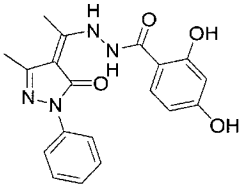
Synthetic Ex. 17 (Compound 3)



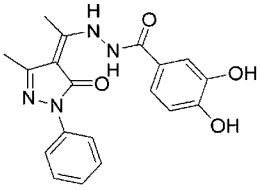
Synthetic Ex. 18 (Compound 58)



Synthetic Ex. 19 (Compound 5)

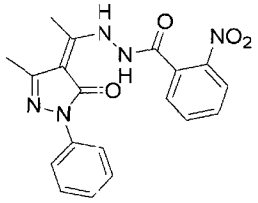


Synthetic Ex. 20 (Compound 4)

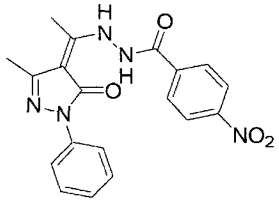


【Ka 10】

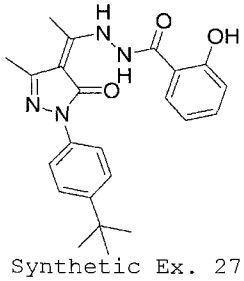
Synthetic Ex. 21
(Compound 59)



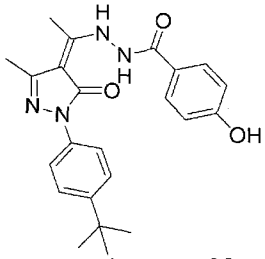
Synthetic Ex. 22
(Compound 60)



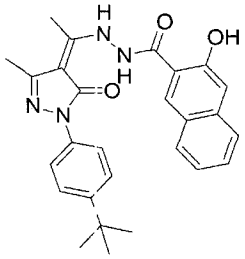
Synthetic Ex. 23
(Compound 61)



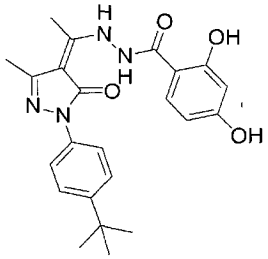
Synthetic Ex. 24
(Compound 63)



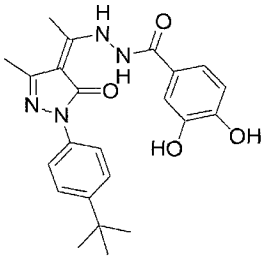
Synthetic Ex. 25
(Compound 119)



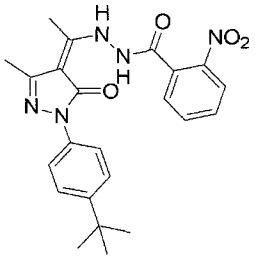
Synthetic Ex. 26
(Compound 65)



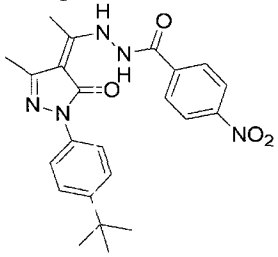
Synthetic Ex. 27
(Compound 64)



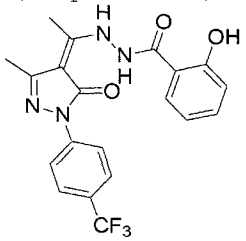
Synthetic Ex. 28
(Compound 120)



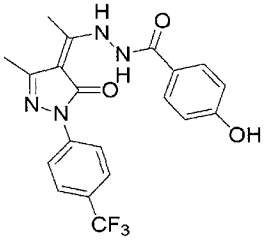
Synthetic Ex. 29
(Compound 121)



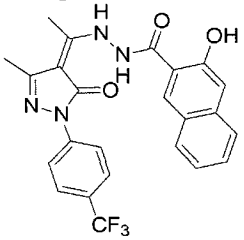
Synthetic Ex. 30
(Compound 370)



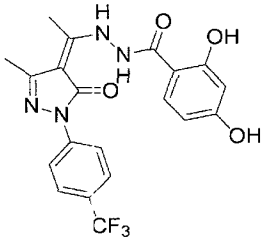
Synthetic Ex. 31
(Compound 372)



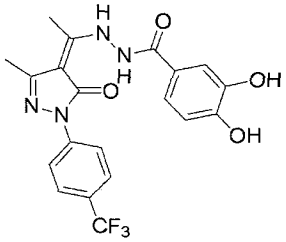
Synthetic Ex. 32
(Compound 428)



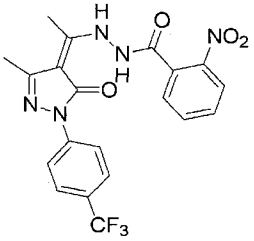
Synthetic Ex. 33
(Compound 374)



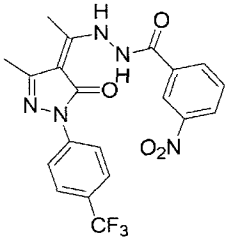
Synthetic Ex. 34
(Compound 373)



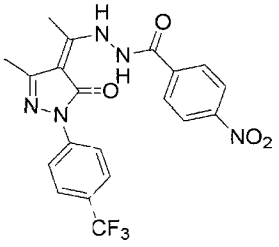
Synthetic Ex. 35
(Compound 429)



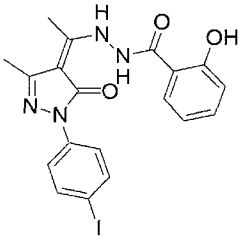
Synthetic Ex. 36
(Compound 378)



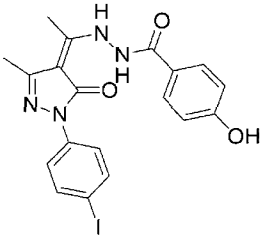
Synthetic Ex. 37
(Compound 430)



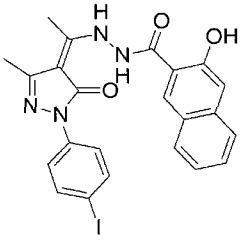
Synthetic Ex. 38
(Compound 249)



Synthetic Ex. 39
(Compound 251)

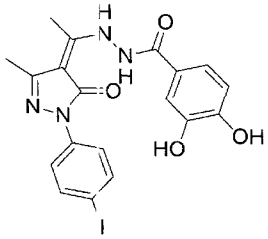


Synthetic Ex. 40
(Compound 306)

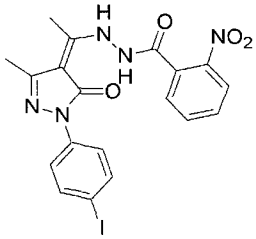


【Ka 11】

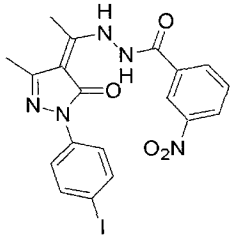
Synthetic Ex. 41
(Compound 252)



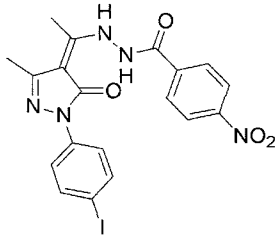
Synthetic Ex. 42
(Compound 307)



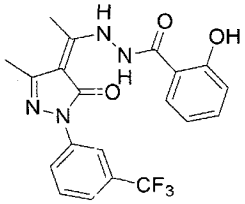
Synthetic Ex. 43
(Compound 257)



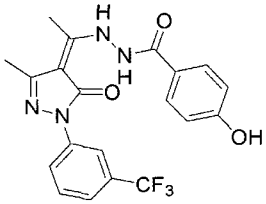
Synthetic Ex. 44
(Compound 308)



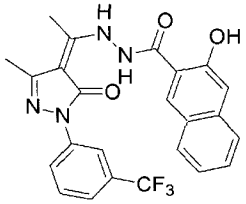
Synthetic Ex. 45
(Compound 309)



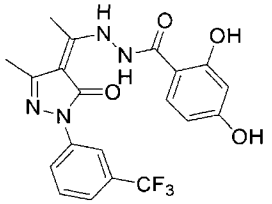
Synthetic Ex. 46
(Compound 311)



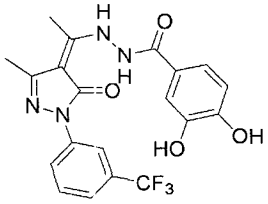
Synthetic Ex. 47
(Compound 367)



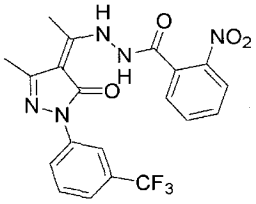
Synthetic Ex. 48
(Compound 313)



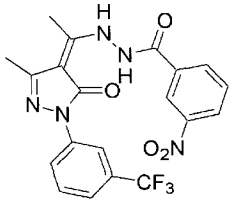
Synthetic Ex. 49
(Compound 312)



Synthetic Ex. 50
(Compound 368)



Synthetic Ex. 51
(Compound 317)



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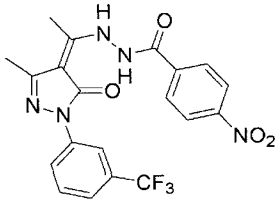
(Compound 369)



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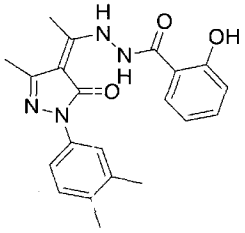
(Compound 124)



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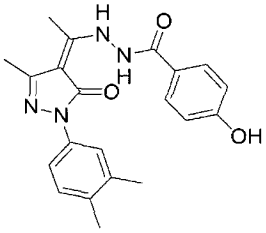
(Compound 126)



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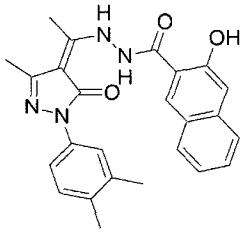
(Compound 182)



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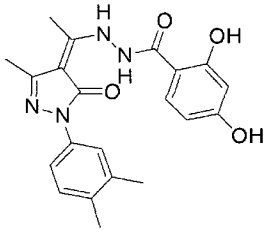
(Compound 128)



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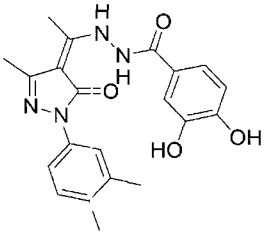
(Compound 127)



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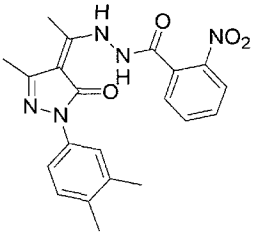
(Compound 183)



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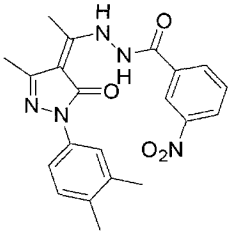
(Compound 132)



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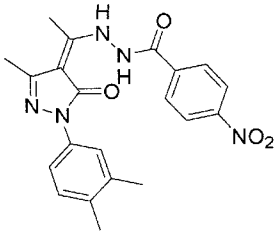
(Compound 184)



【Ka 12】

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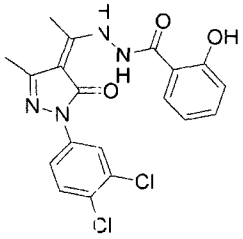

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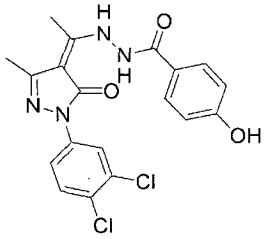
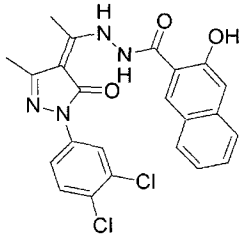
(Compound 189)



Synthetic Ex. 63
(Compound 244)



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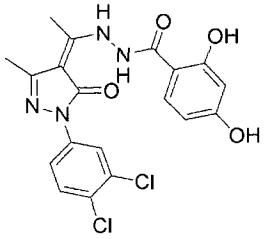
(Compound 191)



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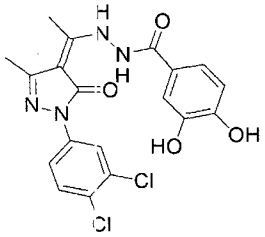
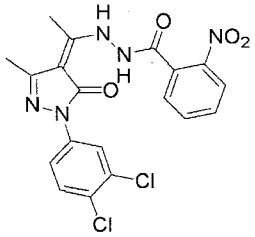
(Compound 190)



Synthetic Ex. 66
(Compound 245)



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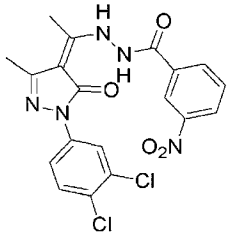
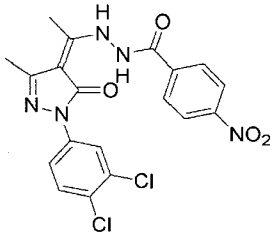
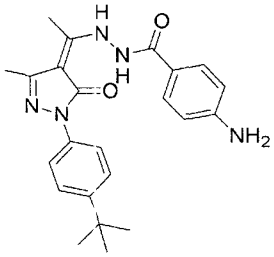
(Compound 195)



Synthetic Ex. 68
(Compound 246)



Synthetic Ex. 69
(Compound 72)



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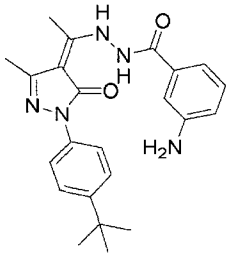
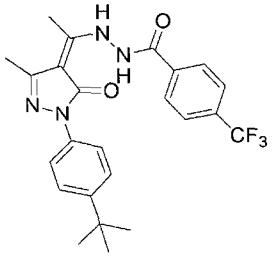
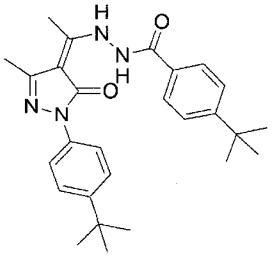
(Compound 71)



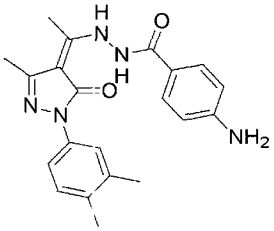
Synthetic Ex. 71
(Compound 122)



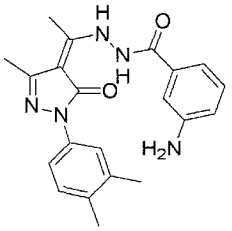
Synthetic Ex. 72
(Compound 123)



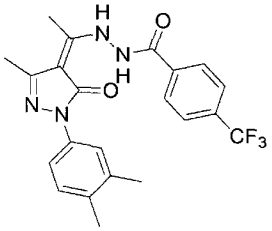
Synthetic Ex. 73
(Compound 135)



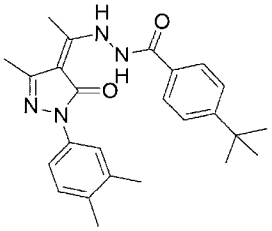
Synthetic Ex. 74
(Compound 134)



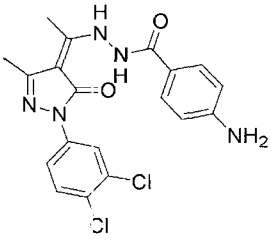
Synthetic Ex. 75
(Compound 185)



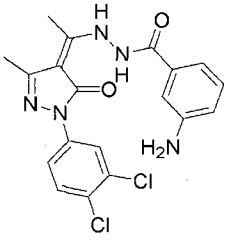
Synthetic Ex. 76
(Compound 186)



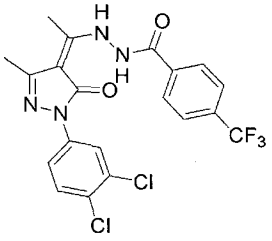
Synthetic Ex. 77
(Compound 198)



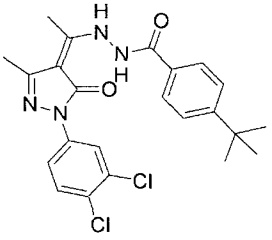
Synthetic Ex. 78
(Compound 197)



Synthetic Ex. 79
(Compound 247)

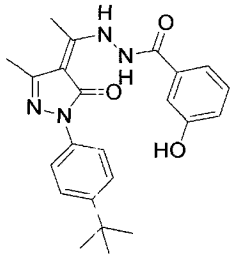


Synthetic Ex. 80
(Compound 248)

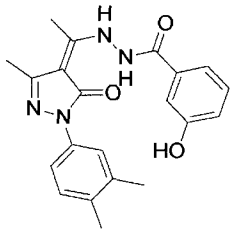


【Ka 13】

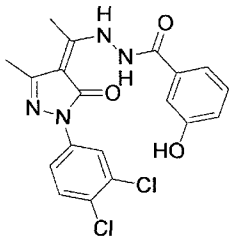
Synthetic Ex. 81
(Compound 62)



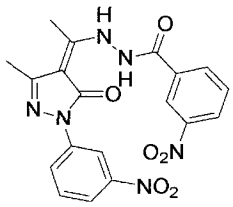
Synthetic Ex. 82
(Compound 125)



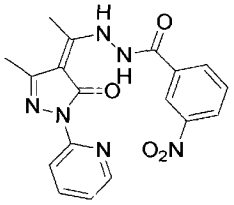
Synthetic Ex. 83
(Compound 188)



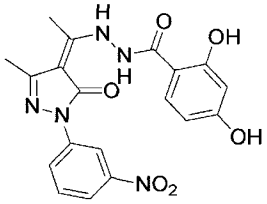
Synthetic Ex. 84
(Compound 944)



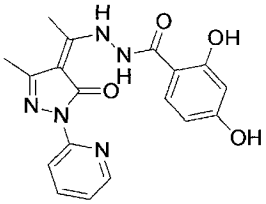
Synthetic Ex. 85
(Compound 947)



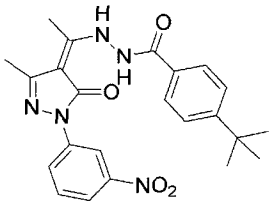
Synthetic Ex. 86
(Compound 945)



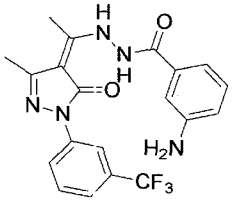
Synthetic Ex. 87
(Compound 948)



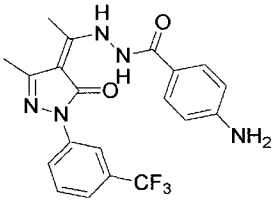
Synthetic Ex. 88
(Compound 946)



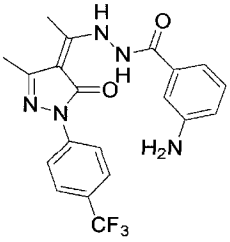
Synthetic Ex. 89
(Compound 319)



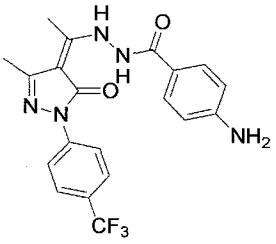
Synthetic Ex. 90
(Compound 320)



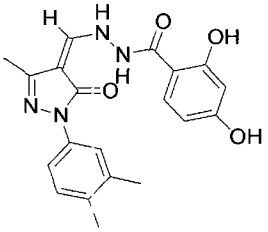
Synthetic Ex. 91
(Compound 380)



Synthetic Ex. 92
(Compound 381)



Synthetic Ex. 93
(Compound 2024)



ASSAY EXAMPLE 1

Stimulation of Proliferation of a Thrombopoietin (TPO)-dependent Cell Line (1)

The reactivity of the compound of Synthetic Example 56 of the present invention (Compound 128), with

thrombopoietin (TPO) receptor was assayed using a human leukemic cell line, UT7/EPO-mpl.

(1) Cells and cell culture

UT7/EPO-mpl is a stable transformed cell line obtained by introducing into human leukemic cell line UT7/EPO a vector that induces expression of human thrombopoietin receptor (*c-mpl*) under control of a cytomegaloviral promoter by the method of Komatsu et al. (J. Biol. Chem, 272:7259-7263 (1997)). Proliferation of this cell line is stimulated by thrombopoietin, while its mother cell line UT7/EPO exhibits no response to thrombopoietin. These two cell lines were subcultured in IMDM medium (GIBCO) containing 10% fetal bovine serum (TRACE SCIENTIFIC) using a CO_2 incubator (5% CO_2, 37°C).

(2) Cell proliferation assay by the MTT method

The subcultured cells described above were washed twice with PBS and suspended in IMDM containing 10% FBS at a cell density of 6×10^4 cells/ml. The cell suspension was transferred to a 96-well tissue culture plate (CORNING) in 100-µl aliquots. Then the compound of Synthetic Example 56 (Compound 128) dissolved in DMSO was diluted 100-fold with IMDM containing 10% fetal bovine serum and added to the aforementioned cell suspension in 20-µl aliquots. The suspension was incubated in a CO_2 incubator (5% CO_2, 37°C) for 4 days. Cell proliferation was assayed according to the method of Mosmann et al. (J. Immunological Methods, 65:55-63 (1983)). A 10-µl aliquot

of 5 mg/ml MTT reagent (SIGMA) was added to each well of the tissue culture plate and the plate was incubated at 37°C for 4 h. The formazan pigment generated was dissolved by adding 150 µl per well of 0.1 N HCl/isopropanol solution and the absorbance of the resulting pigment solution was measured at 550 nm with a 96-well microplate reader (BIO-RAD, M450). Figure 1 shows the results with UT7/EPO-mpl cells, while Figure 2 shows data obtained with UT7/EPO cells expressing no thrombopoietin receptor.

ASSAY EXAMPLE 2

Activity of Signal Transduction Mediated by Thrombopoietin Receptor

The signal-transducing activity of the compound of Synthetic Example 56, the present invention (Compound 128), mediated by thrombopoietin receptor was assayed according to the method of Komatsu et al. (Blood, 87:4552-4560 (1996)). Human leukemic cell line UT7/EPO-mpl was washed three times with PBS and suspended in IMDM containing 10% fetal bovine serum (TRACE SCIENTIFIC) at a cell density of 9×10^5 cells/ml. The cell suspension was incubated in a CO_2 incubator (5% CO_2, 37°C) for 18 h. To 2 ml of this cell suspension (7×10^6 cells/ml), either thrombopoietin (final concentration, 30 ng/ml) or a DMSO solution of the compound of Synthetic Example 56 (Compound 128)(final concentration, 1 µg/ml) was added. After incubating the mixture at 37°C for 1-15 min, the

cells were lysed in 1.4 ml of TNE buffer [20 mM Tris-HCl buffer (pH 7.4) containing 150 mM NaCl, 1 mM EDTA, 1% Triton X-100, 1 mM PMSF, 1 mM Na_3VO_4, and 1/400-diluted Protease Inhibitor Cocktail (SIGMA)]. The cell lysate was centrifuged to collect the supernatant for immunoprecipitation with antibodies against proteins involved in signal transduction [anti-STAT3 (SANTA CRUZ BIOTECHNOLOGY) and anti-STAT5A (UPSTATE BIOTECHNOLOGY)] and protein G Sepharose (PHARMACIA). The immunoprecipitated protein fraction was denatured in a sample buffer for separation by SDS-polyacrylamide gel electrophoresis (7.5%). The separated proteins were transferred onto polyvinylidene difluoride (PVDF) membrane (ATTO, 0.2 μm) at 100 V for 1 h for detection of tyrosine phosphorylation using an alkaline phosphatase-labelled antibody against phosphorylated tyrosine (RC20, TRANSDUCTION LABORATORIES). The antigen-antibody complex formed on the PVDF membrane was visualized with 150 μg/ml NBT (BIO-RAD) and 300 μg/ml BCIP (BIO-RAD). The results are summarized in Table 3.

【Hyo 20】

Table 3

	DMSO	COMPOUND OF SYNTHETIC EXAMPLE 56	Thrombopoietin
STAT 3	-	+	+
STAT 5A	-	+	+

Figure 1 demonstrated that proliferation of UT7/EPO-mpl

cells was stimulated by the compound of Synthetic Example 56 (Compound 128) in a concentration-dependent manner, while no effect of this compound on proliferation was observed with UT7/EPO, the mother cell line, as shown in Figure 2. These results indicate that the compound of Synthetic Example 56 (Compound 128) acts on the thrombopoietin receptor selectively as an activator.

Table 3 shows that the compound Synthetic Example 56 of the present invention (Compound 128) stimulates phosphorylation of STAT3 and STAT5A in the same manner as thrombopoietin does. The results demonstrate that the compound of the present invention shows agonistic action through the same signal transduction as that caused by thrombopoietin.

ASSAY EXAMPLE 3

The following compounds of Synthetic Examples of the present invention were tested according to the method of Assay Example 1 to determine the maximal growth rate (Efficacy), expressed by taking the value with human leukemic cell line UT7/EPO-mpl observed in the presence of 10 ng TPO as 100% standard, and the concentration of each compound that yields a growth rate corresponding to 50% of the maximum cell growth observed with the same compound (EC50). The results are summarized in Table 4.

【Hyo 21】

Table 4

Synthetic Example No.	Efficacy (%)	EC50 (ng/ml)
1	74	7.4
2	89	6.3
3	82	15
4	53	15
5	86	3.4
6	64	7.4
7	99	2.2
8	52	31
9	90	5.1
10	78	20
11	83	2.0
12	100	76
13	99	280
14	91	72
15	109	23
16	58	61
17	73	79
18	94	55
19	100	14
20	91	38
21	39	290
22	50	190
23	129	28
24	89	7.2
25	54	200
26	78	2.9
27	75	5.6
28	99	37
29	67	230
30	106	19
31	63	5.2

32	90	37
33	96	1.1
34	99	5.2
35	99	34
36	97	59
37	63	140
38	93	36
39	97	28
40	37	250
41	115	32
42	71	250
43	87	83
44	26	250
45	74	30
46	82	15
47	48	190
48	62	8.0
49	62	9.1
50	89	37
51	73	33
52	22	120
53	120	12
54	61	7.5
55	53	220
56	96	1.1
57	97	5.9
58	110	32
59	82	24
60	62	100
61	91	29
62	57	6.4
63	21	190
64	74	7.7
65	70	8.9
66	133	33
67	80	33

68	26	210
69	89	5.7
70	87	23
71	89	69
72	88	75
73	84	10
74	77	25
75	89	63
76	79	46
77	78	5.1
78	69	15
79	81	160
80	71	640
81	84	7.2
82	84	26
83	78	6.1
84	109	130
86	105	21
87	71	600
88	70	130
89	68	39
90	76	21
91	81	24
92	82	5.5
93	84	4.3
Reference Synthetic Example 1	7	-
Reference Synthetic Example 2	12	-
Reference Synthetic Example 3	7	-
Reference Synthetic Example 4	67	1400

ASSAY EXAMPLE 4

The compound of Synthetic Example 56 of the present invention (Compound 128), and the compounds (Reference Synthetic Examples 1 to 4) described in WO01/34585, applied by SmithKline Beecham Corp., were tested according to the method of Assay Example 1. Figure 3 shows the results.

FORMULATION EXAMPLE 1

A granule preparation containing the following ingredients is prepared.

Ingredients	
Compound represented by the formula (2)	10 mg
Lactose	700 mg
Corn Starch	274 mg
HPC-L	16 mg
	1000 mg

A compound represented by the formula (2) and lactose are sifted through a 60-mesh sieve. Corn starch is sifted though a 120-mesh sieve. They are mixed in a V-type blender. The powder mixture is kneaded with a low-viscosity hydroxypropylcellulose (HPC-L) aqueous solution, granulated (extrusion granulation, die size 0.5-1 mm) and dried. The resulting dry granules are sifted through a shaking sieve (12/60 mesh) to obtain a granule preparation.

FORMULATION EXAMPLE 2

A powder preparation for capsulation containing the following ingredients is prepared.

Ingredients	
Compound represented by the formula (2)	10 mg
Lactose	79 mg
Corn Starch	10 mg
Magnesium Stearate	1 mg
	100 mg

A compound represented by the formula (2) and lactose are sifted through a 60-mesh sieve. Corn starch is sifted though a 120-mesh sieve. They are mixed with magnesium stearate in a V-type blender. The 10% powder is put in hard capsules No. 5, 100 mg each.

FORMULATION EXAMPLE 3

A granule preparation for capsulation containing the following ingredients is prepared.

Ingredients	
Compound represented by the formula (2)	15 mg
Lactose	90 mg
Corn Starch	42 mg
HPC-L	3 mg
	150 mg

A compound represented by the formula (2) and lactose are sifted through a 60-mesh sieve. Corn starch is sifted though a 120-mesh sieve. They are mixed in a V-type blender. The powder mixture is kneaded with a low-viscosity hydroxypropylcellulose (HPC-L) aqueous solution, granulated (extrusion granulation, die size 0.5-1 mm) and dried. The resulting dry granules are sifted through a shaking sieve (12/60 mesh). The granules are put in hard capsules No. 4, 150 mg each.

FORMULATION EXAMPLE 4

A tablet preparation containing the following ingredients is prepared.

Ingredients	
Compound represented by the formula (2)	10 mg
Lactose	90 mg
Microcrystalline cellulose	30 mg
Magnesium Stearate	5 mg
CMC-Na	15 mg
	150 mg

A compound represented by the formula (2), lactose, microcrystalline cellulose and CMC-Na (carboxymethylcellulose sodium salt) are sifted through a 60-mesh sieve and mixed. The powder mixture is mixed with magnesium stearate to give a bulk powder mixture. The powder mixture is compressed directly into 150 mg tablets.

FORMULATION EXAMPLE 5

An intravenous preparation is prepared as follows.

Compound represented by the formula (2)	100 mg
Saturated Fatty Acid Glyceride	1000 ml

Solutions having the above-mentioned composition are usually administered to a patient intravenously at a rate of 1 ml per 1 minute.

【Effects of the Invention】

The compounds of the present invention which have affinity for thrombopoietin receptor and act as thrombopoietin receptor agonists are useful as preventive, therapeutic and improving agents for diseases against

which activation of the thrombopoietin receptor is effective, especially as drugs for hematological disorders accompanied by abnormal platelet count and as drugs for diseases treated or prevented by stimulating differentiation and proliferation of vascular endothelial cells and endothelial progenitor cells, and are useful as medicines.

【Brief Explanation of the Drawings】

【Fig. 1】

The proliferation of UT7/EPO-mpl cells when stimulated by a compound of the present invention (Synthetic Example 56; Compound 128) assayed by the MTT method.

【Fig. 2】

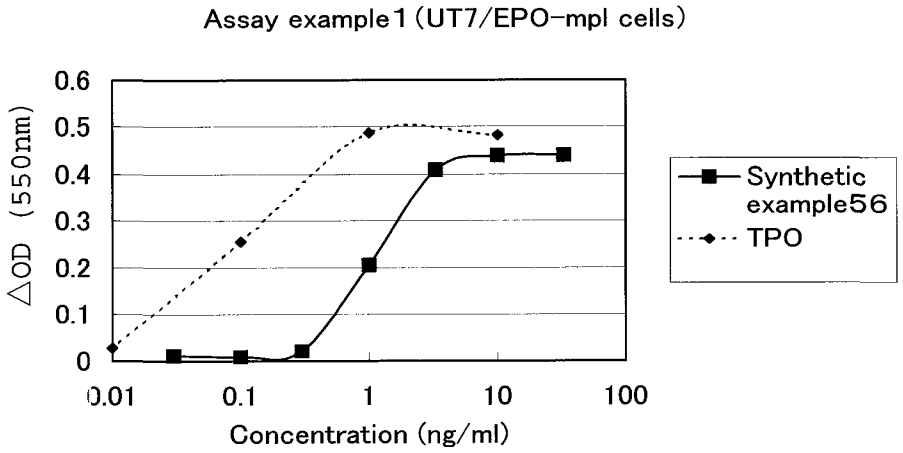
The proliferation of UT7/EPO cells when stimulated by a compound of the present invention (Synthetic Example 56; Compound 128) assayed by the MTT method.

【Fig. 3】

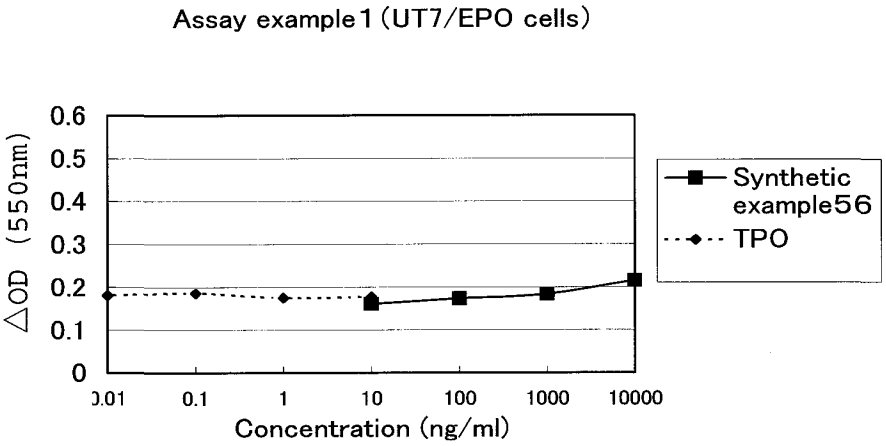
The proliferation of UT7/EPO-mpl cells when stimulated by a compound of the present invention (Synthetic Example 56; Compound 128) or the compounds described in the prior art (Reference Synthetic Examples 1 to 4) assayed by the MTT method.

【TYPE OF DOCUMENT】 DRAWING

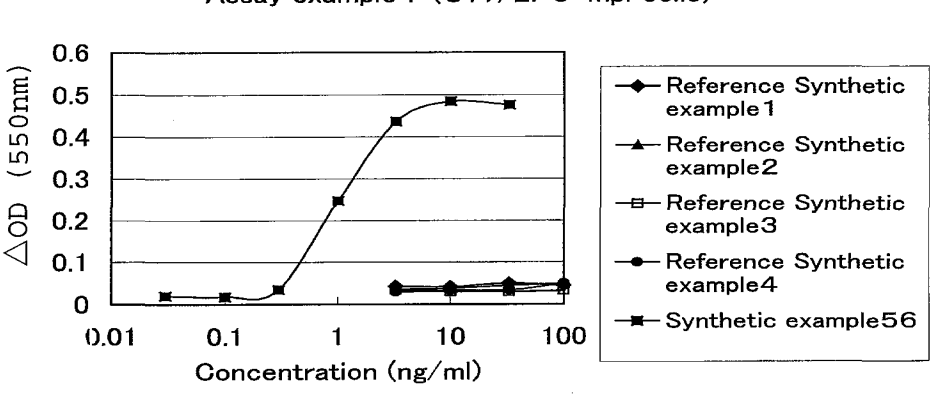
【Fig. 1】



【Fig. 2】



【Fig. 3】



【TYPE OF DOCUMENT】 ABSTRACT

【SUMMARY】

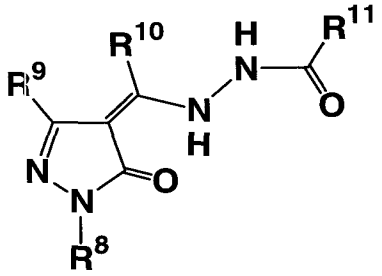
【OBJECT】

To provide a preventive, therapeutic or improving agent for diseases against which activation of the thrombopoietin receptor is effective.

【MEANS OF SOLVING PROBLEMS】

A preventive, therapeutic or improving agent for diseases against which activation of the thrombopoietin receptor is effective or a platelet increasing agent, which contains a thrombopoietin receptor activator represented by the formula (2):

【Ka 1】



(2)

[wherein R^8 is a C_{6-18} aryl group or a pyridyl group, R^9 is hydrogen, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms or a C_{6-18} aryl group, R^{10} is hydrogen, a C_{1-6} alkyl group, a C_{1-3} alkyl group substituted with one or more fluorine atoms, a C_{6-18} aryl group or a pyridyl group, and R^{11} is a C_{6-18} aryl group or a pyridyl group], a tautomer, prodrug or pharmaceutically acceptable salt of the activator or a solvate thereof, as an active ingredient.

【SELECTED FIGURE】 No Selected Figure